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=> d his

     (FILE 'HOME' ENTERED AT 11:46:40 ON 03 FEB 2003)

     FILE 'MEDLINE, PCTFULL, USPATFULL' ENTERED AT 11:46:56 ON 03 FEB 2003
L1         29514 S TRANSGENIC MOUSE
L2          9003 S INOS OR INDUCIBLE NITRIC OXIDE SYNTHASE OR INDUCIBLE NITRIC O
L3            59 S L1 (S) L2
L4          1638 S (KNOCKOUT OR DEFICINET ) (S) L1
L5          1610 S HUMAN (S) L2
L6             2 S L4 (S) L5
L7             9 S L4 (L) L5
L8            59 DUP REM L3 (0 DUPLICATES REMOVED)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, PCTFULL, USPATFULL, CONFSCI,
     SCISEARCH' ENTERED AT 11:54:36 ON 03 FEB 2003
L9           244 S L3
L10            9 S L6
L11          244 S L9
L12           16 S L7
L13           10 DUP REM L10 L12 (15 DUPLICATES REMOVED)
L14           86 DUP REM L11 (158 DUPLICATES REMOVED)
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 NEWS  2  Apr 08   "Ask CAS" for self-help around the clock
 NEWS  3  Apr 09   BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09   ZDB will be removed from STN
 NEWS  5  Apr 19   US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22   Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22   BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22   Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03   New e-mail delivery for search results now available
 NEWS 10  Jun 10   MEDLINE Reload
 NEWS 11  Jun 10   PCTFULL has been reloaded
 NEWS 12  Jul 02   FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22   USAN to be reloaded July 28, 2002;
                   saved answer sets no longer valid
 NEWS 14  Jul 29   Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30   NETFIRST to be removed from STN
 NEWS 16  Aug 08   CANCERLIT reload
 NEWS 17  Aug 08   PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08   NTIS has been reloaded and enhanced
 NEWS 19  Aug 19   Aquatic Toxicity Information Retrieval (AQUIRE)
                   now available on STN
 NEWS 20  Aug 19   IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19   The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26   Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03   JAPIO has been reloaded and enhanced
 NEWS 24  Sep 16   Experimental properties added to the REGISTRY file
 NEWS 25  Sep 16   CA Section Thesaurus available in CAPLUS and CA
 NEWS 26  Oct 01   CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 27  Oct 21   EVENTLINE has been reloaded
 NEWS 28  Oct 24   BEILSTEIN adds new search fields
 NEWS 29  Oct 24   Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 30  Oct 25   MEDLINE SDI run of October 8, 2002
 NEWS 31  Nov 18   DKILIT has been renamed APOLLIT
 NEWS 32  Nov 25   More calculated properties added to REGISTRY
 NEWS 33  Dec 02   TIBKAT will be removed from STN
 NEWS 34  Dec 04   CSA files on STN
 NEWS 35  Dec 17   PCTFULL now covers WP/PCT Applications from 1978 to date
 NEWS 36  Dec 17   TOXCENTER enhanced with additional content
 NEWS 37  Dec 17   Adis Clinical Trials Insight now available on STN
 NEWS 38  Dec 30   ISMEC no longer available
 NEWS 39  Jan 13   Indexing added to some pre-1967 records in CA/CAPLUS
 NEWS 40  Jan 21   NUTRACEUT offering one free connect hour in February 2003
 NEWS 41  Jan 21   PHARMAML offering one free connect hour in February 2003
 NEWS 42  Jan 29   Simultaneous left and right truncation added to COMPENDEX,
                   ENERGY, INSPEC

 NEWS EXPRESS  January 6 CURRENT WINDOWS VERSION IS V6.01a,
               CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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 NEWS WWW       CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 11:46:40 ON 03 FEB 2003

=> file medline pctful uspatful
COST IN U.S. DOLLARS                                 SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      0.21       0.21

FILE 'MEDLINE' ENTERED AT 11:46:56 ON 03 FEB 2003

FILE 'PCTFULL' ENTERED AT 11:46:56 ON 03 FEB 2003
COPYRIGHT (C) 2003 Univentio

FILE 'USPATFULL' ENTERED AT 11:46:56 ON 03 FEB 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> s transgenic mouse
L1       29514 TRANSGENIC MOUSE

=> s inos or inducible nitric oxide synthase or inducible nitric oxide synthetase
L2        9003 INOS OR INDUCIBLE NITRIC OXIDE SYNTHASE OR INDUCIBLE NITRIC
               OXIDE SYNTHETASE

=> s l1 (S) l2
L3          59 L1 (S) L2

=> s human
SYSTEM LIMITS EXCEEDED - SEARCH ENDED
   1 FILES SEARCHED...
COMMAND INTERRUPTED
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Desk by telephone or via SEND in the STNMAIL file.

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     (FILE 'HOME' ENTERED AT 11:46:40 ON 03 FEB 2003)

     FILE 'MEDLINE, PCTFULL, USPATFULL' ENTERED AT 11:46:56 ON 03 FEB 2003
L1         29514 S TRANSGENIC MOUSE
L2          9003 S INOS OR INDUCIBLE NITRIC OXIDE SYNTHASE OR INDUCIBLE NITRIC O
L3            59 S L1 (S) L2

=> s (knockout or deficinet ) (S) l1
L4         1638 (KNOCKOUT OR DEFICINET ) (S) L1
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=> s human (S) l2
L5        1610 HUMAN (S) L2

=> s l4 (S) l5
L6           2 L4 (S) L5

=> d 1-2 ibib abs

L6   ANSWER 1 OF 2     MEDLINE
ACCESSION NUMBER:    2002633269     MEDLINE
DOCUMENT NUMBER:     22267125   PubMed ID: 12379707
TITLE:               Interleukin-10 (IL-10) in experimental visceral
                     leishmaniasis and IL-10 receptor blockade as immunotherapy.
AUTHOR:              Murray Henry W; Lu Christina M; Mauze Smita; Freeman
                     Sherry; Moreira Andre L; Kaplan Gilla; Coffman Robert L
CORPORATE SOURCE:    Department of Medicine, Weill Medical College of Cornell
                     University, New York, New York 10021, USA..
                     hwmurry@med.cornell.edu
CONTRACT NUMBER:     AI16963 (NIAID)
     AI22616 (NIAID)
SOURCE:              INFECTION AND IMMUNITY, (2002 Nov) 70 (11) 6284-93.
                     Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200211
ENTRY DATE:          Entered STN: 20021024
                     Last Updated on STN: 20021213
                     Entered Medline: 20021108
AB   Interleukin-10 (IL-10) is thought to promote intracellular infection,
     including human visceral leishmaniasis, by disabling Th1
     cell-type responses and/or deactivating parasitized tissue macrophages. To
     develop a rationale for IL-10 inhibition as treatment in visceral
     infection, Th1 cytokine-driven responses were characterized in Leishmania
     donovani-infected BALB/c mice in which IL-10 was absent or overexpressed
     or its receptor (IL-10R) was blockaded. IL-10 knockout and
     normal mice treated prophylactically with anti-IL-10R demonstrated
     accelerated granuloma assembly and rapid parasite killing without untoward
     tissue inflammation; IL-12 and gamma interferon mRNA expression,
     inducible nitric oxide synthase
     reactivity, and responsiveness to antimony chemotherapy were also enhanced
     in knockout mice. In IL-10 transgenic mice,
     parasite replication was unrestrained, and except for antimony
     responsiveness, measured Th1 cell-dependent events were all initially
     impaired. Despite subsequent granuloma assembly, high-level infection
     persisted, and antimony-treated transgenic mice also
     relapsed. In normal mice with established infection, anti-IL-10R treatment
     was remarkably active, inducing near-cure by itself and synergism with
     antimony. IL-10's deactivating effects regulate outcome in experimental
     visceral leishmaniasis, and IL-10R blockade represents a potential immuno-
     and/or immunochemotherapeutic approach in this infection.

L6   ANSWER 2 OF 2     MEDLINE
ACCESSION NUMBER:    2002408347     IN-PROCESS
DOCUMENT NUMBER:     22152065   PubMed ID: 12162464
TITLE:               Upregulation of phosphoinositide 3-kinase and protein
                     kinase B in alveolar macrophages following ozone
                     inhalation. role of NF-kappaB and STAT-1 in ozone-induced
                     nitric oxide production and toxicity.
AUTHOR:              Laskin Debra L; Fakhrzadeh Ladan; Heck Diane E; Gerecke
                     Donald; Laskin Jeffrey D
CORPORATE SOURCE:    Environmental and Occupational Health Sciences Institute,
                     Rutgers University and University of Medicine and Dentistry
                     of New Jersey, Piscataway, USA.. laskin@eohsi.rutgers.edu
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CONTRACT NUMBER: ES04738 (NIEHS)
ES05022 (NIEHS)
ES06897 (NIEHS)
GM34310 (NIGMS)
HL67708 (NHLBI)
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (2002 May-Jun) 234-235 (1-2) 91-8.
Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20021212

AB Inhalation of toxic doses of ozone causes lung injury and inflammation in **humans** and experimental animals. Using a rodent model of ozone toxicity, we have previously demonstrated that macrophages recruited to the lung following exposure to this oxidant contribute to the pathogenesis of tissue injury. In the present studies we analyzed potential mechanisms regulating alveolar macrophage activity following ozone inhalation and the role of inflammatory mediators in toxicity. Treatment of mice with ozone (0.8 ppm, 3 h) resulted in increased expression of **inducible nitric oxide synthase** (**iNOS**) protein and production of nitric oxide (NO) and peroxynitrite by alveolar macrophages. In contrast, these effects were not observed in macrophages from **transgenic mice** with a targeted disruption of the gene for **iNOS**, or in mice overexpressing superoxide dismutase. Moreover, ozone toxicity, as measured by bronchoalveolar lavage protein levels and nitrotyrosine staining of the lung was prevented in both of these **transgenic mouse** strains. The promoter/enhancer region of the **iNOS** gene contains binding sites for the transcription factors NF-kappaB and STAT-1 which regulate the activity of the gene. Ozone inhalation resulted in a rapid and prolonged activation of NF-kappaB in alveolar macrophages. Phosphoinositide 3-kinase (PI 3-K) and its down stream target, protein kinase B (PKB), which are known to regulate NF-kappaB activity, also increased in alveolar macrophages following ozone inhalation. These data, together with our findings that inhibitors of PI 3-K block NO production, suggest that these proteins are important in controlling expression of **iNOS**. Furthermore, the fact that macrophages from NF-kappaB p50 **knockout** mice did not generate reactive nitrogen intermediates and that these mice were protected from ozone induced toxicity demonstrate the importance of the NF-kappaB signaling pathway in lung injury. We also found that STAT-1 nuclear binding activity and STAT-1 protein expression were upregulated in macrophages from ozone treated animals. Taken together, these data suggest that biochemical signaling pathways that control the expression of genes critical for the inflammatory process play a role in ozone toxicity.

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L1 29514 S TRANSGENIC MOUSE
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L3 59 S L1 (S) L2
L4 1638 S (KNOCKOUT OR DEFICINET) (S) L1
L5 1610 S HUMAN (S) L2
L6 2 S L4 (S) L5

=> s l4 (l) l5
L7 9 L4 (L) L5

=> d 1-9 ibib abs

L7 ANSWER 1 OF 9 MEDLINE
ACCESSION NUMBER: 2002633269 MEDLINE
DOCUMENT NUMBER: 22267125 PubMed ID: 12379707
TITLE: Interleukin-10 (IL-10) in experimental visceral leishmaniasis and IL-10 receptor blockade as immunotherapy.
AUTHOR: Murray Henry W; Lu Christina M; Mauze Smita; Freeman Sherry; Moreira Andre L; Kaplan Gilla; Coffman Robert L
CORPORATE SOURCE: Department of Medicine, Weill Medical College of Cornell University, New York, New York 10021, USA.. hwmurry@med.cornell.edu
CONTRACT NUMBER: AI16963 (NIAID)
AI22616 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (2002 Nov) 70 (11) 6284-93. Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20021213
Entered Medline: 20021108

AB Interleukin-10 (IL-10) is thought to promote intracellular infection, including **human** visceral leishmaniasis, by disabling Th1 cell-type responses and/or deactivating parasitized tissue macrophages. To develop a rationale for IL-10 inhibition as treatment in visceral infection, Th1 cytokine-driven responses were characterized in Leishmania donovani-infected BALB/c mice in which IL-10 was absent or overexpressed or its receptor (IL-10R) was blockaded. IL-10 **knockout** and normal mice treated prophylactically with anti-IL-10R demonstrated accelerated granuloma assembly and rapid parasite killing without untoward tissue inflammation; IL-12 and gamma interferon mRNA expression, **inducible nitric oxide synthase** reactivity, and responsiveness to antimony chemotherapy were also enhanced in **knockout** mice. In IL-10 **transgenic mice**, parasite replication was unrestrained, and except for antimony responsiveness, measured Th1 cell-dependent events were all initially impaired. Despite subsequent granuloma assembly, high-level infection persisted, and antimony-treated **transgenic mice** also relapsed. In normal mice with established infection, anti-IL-10R treatment was remarkably active, inducing near-cure by itself and synergism with antimony. IL-10's deactivating effects regulate outcome in experimental visceral leishmaniasis, and IL-10R blockade represents a potential immuno- and/or immunochemotherapeutic approach in this infection.

L7 ANSWER 2 OF 9 MEDLINE
ACCESSION NUMBER: 2002408347 IN-PROCESS
DOCUMENT NUMBER: 22152065 PubMed ID: 12162464
TITLE: Upregulation of phosphoinositide 3-kinase and protein kinase B in alveolar macrophages following ozone inhalation. role of NF-kappaB and STAT-1 in ozone-induced nitric oxide production and toxicity.
AUTHOR: Laskin Debra L; Fakhrzadeh Ladan; Heck Diane E; Gerecke Donald; Laskin Jeffrey D
CORPORATE SOURCE: Environmental and Occupational Health Sciences Institute, Rutgers University and University of Medicine and Dentistry of New Jersey, Piscataway, USA.. laskin@eohsi.rutgers.edu
CONTRACT NUMBER: ES04738 (NIEHS)
ES05022 (NIEHS)
ES06897 (NIEHS)
GM34310 (NIGMS)
HL67708 (NHLBI)
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (2002 May-Jun) 234-235 (1-2) 91-8.

Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20021212

AB Inhalation of toxic doses of ozone causes lung injury and inflammation in **humans** and experimental animals. Using a rodent model of ozone toxicity, we have previously demonstrated that macrophages recruited to the lung following exposure to this oxidant contribute to the pathogenesis of tissue injury. In the present studies we analyzed potential mechanisms regulating alveolar macrophage activity following ozone inhalation and the role of inflammatory mediators in toxicity. Treatment of mice with ozone (0.8 ppm, 3 h) resulted in increased expression of **inducible nitric oxide synthase** (**iNOS**) protein and production of nitric oxide (NO) and peroxynitrite by alveolar macrophages. In contrast, these effects were not observed in macrophages from **transgenic mice** with a targeted disruption of the gene for **iNOS**, or in mice overexpressing superoxide dismutase. Moreover, ozone toxicity, as measured by bronchoalveolar lavage protein levels and nitrotyrosine staining of the lung was prevented in both of these **transgenic mouse** strains. The promoter/enhancer region of the **iNOS** gene contains binding sites for the transcription factors NF-kappaB and STAT-1 which regulate the activity of the gene. Ozone inhalation resulted in a rapid and prolonged activation of NF-kappaB in alveolar macrophages. Phosphoinositide 3-kinase (PI 3-K) and its down stream target, protein kinase B (PKB), which are known to regulate NF-kappaB activity, also increased in alveolar macrophages following ozone inhalation. These data, together with our findings that inhibitors of PI 3-K block NO production, suggest that these proteins are important in controlling expression of **iNOS**. Furthermore, the fact that macrophages from NF-kappaB p50 **knockout** mice did not generate reactive nitrogen intermediates and that these mice were protected from ozone induced toxicity demonstrate the importance of the NF-kappaB signaling pathway in lung injury. We also found that STAT-1 nuclear binding activity and STAT-1 protein expression were upregulated in macrophages from ozone treated animals. Taken together, these data suggest that biochemical signaling pathways that control the expression of genes critical for the inflammatory process play a role in ozone toxicity.

L7 ANSWER 3 OF 9 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2002103031 PCTFULL ED 20030115 EW 200252
TITLE (ENGLISH): METHODS FOR DETECTING AND TREATING THE EARLY ONSET OF AGING-RELATED CONDITIONS
TITLE (FRENCH): METHODES DE DETECTION ET DE TRAITEMENT DE L'APPARITION PRECOCE D'ETATS LIES AU VIEILLISSEMENT
INVENTOR(S): BARNETT, Katherine; CROSSMAN, David, C.; DUFF, Gordon, W.; FRANCIS, Sheila, E.; KORNMAN, Kenneth, S.
PATENT ASSIGNEE(S): INTERLEUKIN GENETICS, INC.
AGENT: QUISEL, John, D.
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002103031	A2	20021227

DESIGNATED STATES AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL

PT SE TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-US19205 A 20020617
PRIORITY INFO.: US 2001-60/298,493 20010615

ABEN Certain aspects of the invention relate to methods for determining a subject's susceptibility to the early onset or progression of aging-related conditions. In certain aspects the invention relates to accessing the genotype of a subject with respect to an allele of IL-1 pattern 1, pattern 2 and/or pattern 3. In other aspect, the invention relates to methods for selecting a therapeutic regimen, identifying age-related biomarkers, monitoring the progress of age-related conditions and identifying therapeutics for delaying or diminishing the onset of aging-related conditions.

ABFR Certains modes de realisation de l'invention concernent des methodes de determination de la receptivite d'un sujet a l'apparition precoce ou a la progression d'etats lies au vieillissement. Certains modes de realisation de l'invention concernent l'acces au genotype d'un sujet par rapport a un allele de l'interleukine-1 (IL-1) modele 1, modele 2 et/ou modele 3. Dans un autre mode de realisation, l'invention concerne des methodes de selection d'un regime therapeutique, d'identification de marqueurs biologiques lies au vieillissement, de surveillance de la progression d'etats lies au vieillissement et d'identification de therapies permettant de retarder ou de diminuer l'apparition d'etats lies au vieillissement.

L7 ANSWER 4 OF 9 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2002101015 PCTFULL ED 20030102 EW 200251
TITLE (ENGLISH): INTEGRATIVE ASSAYS FOR MONITORING MOLECULAR ASSEMBLY EVENTS
TITLE (FRENCH): TECHNIQUES D'ESSAIS INTEGRATIFS POUR LE CONTROLE D'EVENEMENTS D'ASSEMBLAGE MOLECULAIRE
INVENTOR(S): DOWER, Steven; DUFF, Gordon, W.
PATENT ASSIGNEE(S): INTERLEUKIN GENETICS, INC.
AGENT: OLESEN, James, T.
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002101015	A2	20021219

DESIGNATED STATES AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

APPLICATION INFO.: WO 2002-US18346 A 20020611
PRIORITY INFO.: US 2001-60/297,305 20010611

ABEN The invention relates to methods, compositions, and apparatus for monitoring molecular assembly events. Monitoring such molecular assembly events, in combination with other assays such as genetic screening, permits the dissection of genetic and nongenetic influences on a particular biological activity.

ABFR L'invention concerne des procedes, des compositions et un appareil destines a controler des evenements d'assemblage moleculaire. Le controle de tels evenements d'assemblage moleculaire, combine avec d'autres essais comme le depistage genetique, permet d'analyser l'existence d'influences genetiques ou autres sur une activite biologique particuliere.

L7 ANSWER 5 OF 9 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2001060408 PCTFULL ED 20020822
TITLE (ENGLISH): MICROCOMPETITON AND HUMAN DISEASE
TITLE (FRENCH): MICRO-COMPETITION ET MALADIE HUMAINE
INVENTOR(S): POLANSKY, Hanan
PATENT ASSIGNEE(S): SCI PHARMACEUTICALS, INC.; POLANSKY, Hanan
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2001060408	A2	20010823
DESIGNATED STATES	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2001-US5314	A	20010216
PRIORITY INFO.:	US 2000-60/183,184		20000217
	US 2000-09/732,360		20001207

ABEN Cellular microcompetition for the transcription factor human GA binding protein (GABP) is a risk factor associated with obesity and obesity-related diseases such as osteoarthritis, atherosclerosis, obstructive sleep apnea, various cancers, and periodontitis. The invention uses this novel discovery to develop assays which determine the level of microcompetition in a cell. Other assays developed from the knowledge that microcompetition is occurring in cells are also disclosed. This novel discovery led to the development of assays which can determine the level of microcompetition in a cell and to select compounds to target this microcompetition syndrome. In addition, methods to treat a patient for microcompetition based disease are taught.

ABFR La micro-competition cellulaire pour la proteine humaine de fixation GA du facteur de transcription (GABP) est un facteur de risque associe a l'obesite et a des troubles lies a l'obesite tels que l'arthrose, l'atherosclerose, l'apnee obstructive, divers cancers et la parodontite. Cette decouverte permet de mettre au point des epreuves biologiques aux fins de la determination de l'importance de la micro-competition dans une cellule. L'invention porte egalement sur d'autres epreuves mises au point a partir de la connaissance du fait que cette micro-competition survient dans des cellules. Cette invention debouche sur la mise au point d'epreuves biologiques permettant de determiner l'importance de la micro-competition dans une cellule et de selectionner des composes permettant de cibler le syndrome de la micro-competition. L'invention concerne, de surcroit, des methodes de traitement de patients souffrant de troubles lies a la micro-competition.

L7 ANSWER 6 OF 9 PCTFULL COPYRIGHT 2003 Univentio

ACCESSION NUMBER: 2000060117 PCTFULL ED 20020515

TITLE (ENGLISH): PREDICTION OF RISK OF INTERSTITIAL LUNG DISEASE

TITLE (FRENCH): PREDICTION DES RISQUES DE PATHOLOGIE INTERSTITIELLE PULMONAIRE

INVENTOR(S): DUFF, Gordon, W.; DI GIOVINE, Francesco, Saverio; WHYTE, Moria

PATENT ASSIGNEE(S): INTERLEUKIN GENETICS, INC.; DUFF, Gordon, W.; DI GIOVINE, Francesco, Saverio; WHYTE, Moria

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000060117	A2	20001012
DESIGNATED STATES	AE AU BR CA CN CZ HU IL JP KR MX NO NZ PL RU SG TR US YU ZA AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 2000-US8492	A	20000331
PRIORITY INFO.:	US 1999-09/286,108		19990402

ABEN The present invention provides novel methods and kits for determining whether a subject has or
is likely to develop an interstitial lung disorder such as pulmonary fibrosis; as well as methods
for treating an ILD and screening assays for identifying novel ILD

therapeutics.

ABFR L'invention concerne des methodes et des kits nouveaux permettant de determiner si un sujet est atteint d'une pathologie interstitielle pulmonaire ou s'il est susceptible de developper une telle pathologie, telle que la fibrose pulmonaire. L'invention concerne egalement des methodes de traitement d'une pathologie interstitielle pulmonaire et des essais de criblage pour identifier de nouvelles therapeutiques contre ces pathologies.

L7 ANSWER 7 OF 9 PCTFULL COPYRIGHT 2003 Univentio

ACCESSION NUMBER: 1997033989 PCTFULL ED 20020514

TITLE (ENGLISH): TRANSGENIC ANIMALS HAVING A DISRUPTED eNOS GENE AND USE THEREOF

TITLE (FRENCH): ANIMAUX TRANSGENIQUES PRESENTANT UN GENE eNOS A ACTIVITE PERTURBEE ET LEUR UTILISATION

INVENTOR(S): HUANG, Paul, L.; FISHMAN, Mark, C.; MOSKOWITZ, Michael, A.

PATENT ASSIGNEE(S): THE GENERAL HOSPITAL CORPORATION

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9733989	A1	19970918
DESIGNATED STATES	CA JP MX AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1997-US4184	A	19970314
PRIORITY INFO.:	US 1996-60/013,525		19960315
	US 1996-60/027,362		19960918

ABEN This invention relates to transgenic non-human animals comprising a disrupted endothelial nitric oxide synthase gene. These animals exhibit abnormal wound-healing properties and hypertension. This invention also relates to methods of using the transgenic animals to screen for compounds having a potential therapeutic utility for vascular endothelial disorders, such as hypertension, cerebral ischemia or stroke, atherosclerosis and wound-healing activities. Moreover, this invention also relates to methods of treating a patient suffering from hypertension and wound-healing abnormalities with the compounds identified using the transgenic animals, and methods of making the transgenic animals. A method of treating a wound using nitroglycerin is also provided.

ABFR L'invention porte sur des animaux transgeniques presentant un gene endothelial de la synthase de l'oxyde nitrique (eNOS) a activite perturbee. Ces animaux presentent une cicatrisation anormale et de l'hypertension. L'invention porte egalement sur des methodes d'utilisation desdits animaux transgeniques pour detecter certains composes presentant une utilite therapeutique potentielle vis-a-vis des troubles vasculaires endotheliaux tels que l'hypertension, l'ischemie et les attaques cerebrales, l'atherosclerose, et le processus de cicatrisation. L'invention porte de plus sur des procedes de traitement de patients souffrant d'hypertension et d'anomalies de cicatrisation par des composes identifies en utilisant des animaux transgeniques, et sur des procedes de creation d'animaux transgeniques. L'invention porte enfin sur un procede de traitement des plaies a l'aide de

nitroglycerine.

L7 ANSWER 8 OF 9 USPATFULL
ACCESSION NUMBER: 2002:331268 USPATFULL
TITLE: Osteopontin knock-out mouse and methods of use thereof
INVENTOR(S): Denhardt, David T., Bridgewater, NJ, UNITED STATES
Rittling, Susan R., Kingston, NJ, UNITED STATES
Noda, Masaki, Tokyo, JAPAN
Kowalski, Aaron J., Piscataway, NJ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002188962	A1	20021212
APPLICATION INFO.:	US 2002-188884	A1	20020702 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-340484, filed on 30 Jun 1999, GRANTED, Pat. No. US 6414219

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-91200P	19980630 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DANN DORFMAN HERRELL & SKILLMAN, SUITE 720, 1601 MARKET STREET, PHILADELPHIA, PA, 19103-2307
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 1586
AB A transgenic non-human animal with alterations in the osteopontin gene is prepared by introduction of a gene encoding an altered osteopontin protein into a host non-human animal. Methods for using transgenic mice so generated to screen for agents that effect osteopontin's cellular modulating activity are also provided.

L7 ANSWER 9 OF 9 USPATFULL
ACCESSION NUMBER: 2001:191334 USPATFULL
TITLE: Endothelial NOS knockout mice and methods of use
INVENTOR(S): Huang, Paul L., Boston, MA, United States
Fishman, Mark C., Newton Center, MA, United States
Moskowitz, Michael A., Belmont, MA, United States
PATENT ASSIGNEE(S): The General Hospital Corporation, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6310270	B1	20011030
APPLICATION INFO.:	US 1997-818082		19970314 (8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-13525P	19960315 (60)
	US 1996-27362P	19960918 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Martin, Jill D.
ASSISTANT EXAMINER: Baker, Anne-Marie
LEGAL REPRESENTATIVE: Sterne, Kessler, Goldstein & Fox P.L.L.C.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 53 Drawing Figure(s); 24 Drawing Page(s)
LINE COUNT: 2949
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to transgenic non-human animals comprising a disrupted endothelial nitric oxide synthase gene. These animals exhibit

abnormal wound-healing properties and hypertension. This invention also relates to methods of using the transgenic animals to screen for compounds having a potential therapeutic utility for vascular endothelial disorders, such as hypertension, cerebral ischemia or stroke, atherosclerosis and wound-healing activities. Moreover, this invention also relates to methods of treating a patient suffering from hypertension and wound-healing abnormalities with the compounds identified using the transgenic animals, and methods of making the transgenic animals. A method of treating a wound using nitroglycerin is also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d his

(FILE 'HOME' ENTERED AT 11:46:40 ON 03 FEB 2003)

FILE 'MEDLINE, PCTFULL, USPATFULL' ENTERED AT 11:46:56 ON 03 FEB 2003
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L2 9003 S INOS OR INDUCIBLE NITRIC OXIDE SYNTHASE OR INDUCIBLE NITRIC O
L3 59 S L1 (S) L2
L4 1638 S (KNOCKOUT OR DEFICINET) (S) L1
L5 1610 S HUMAN (S) L2
L6 2 S L4 (S) L5
L7 9 S L4 (L) L5

=> dup rem l3
PROCESSING COMPLETED FOR L3
L8 59 DUP REM L3 (0 DUPLICATES REMOVED)

=> file medline caplus biosis embase pctful uspatful confsci scisearch
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 16.54 16.75

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CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

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=> s l3 l6 l7
MISSING OPERATOR L3 L6
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

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=> s l3
L9          244 L3

=> s l6
   4 FILES SEARCHED...
L10           9 L6

=> s l9
L11         244 L3

=> s l7
   4 FILES SEARCHED...
L12          16 L7

=> dup rem l10 l12
PROCESSING COMPLETED FOR L10
PROCESSING COMPLETED FOR L12
L13           10 DUP REM L10 L12 (15 DUPLICATES REMOVED)

=> d 1-10 ibib abs

L13    ANSWER 1 OF 10    PCTFULL   COPYRIGHT 2003 Univentio
ACCESSION NUMBER:        2002103031 PCTFULL  ED 20030115  EW 200252
TITLE (ENGLISH):         METHODS FOR DETECTING AND TREATING THE EARLY ONSET OF
                         AGING-RELATED CONDITIONS
TITLE (FRENCH):          METHODES DE DETECTION ET DE TRAITEMENT DE L'APPARITION
                         PRECOCE D'ETATS LIES AU VIEILLISSEMENT
INVENTOR(S):             BARNETT, Katherine; CROSSMAN, David, C.; DUFF, Gordon,
                         W.; FRANCIS, Sheila, E.; KORNMAN, Kenneth, S.
PATENT ASSIGNEE(S):      INTERLEUKIN GENETICS, INC.
AGENT:                   QUISEL, John, D.
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2002103031         A2 20021227
DESIGNATED STATES        AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
                         CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                         IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
                         MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
                         SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW GH GM
                         KE LS MW MZ SD SL SZ TZ UG ZM ZW AM AZ BY KG KZ MD RU
                         TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL
                         PT SE TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD
                         TG
APPLICATION INFO.:       WO 2002-US19205      A  20020617
PRIORITY INFO.:          US 2001-60/298,493      20010615
ABEN   Certain aspects of the invention relate to methods for determining a
       subject's susceptibility to the early onset or progression of
       aging-related conditions. In certain aspects the invention relates to
       accessing the genotype of a subject with respect to an allele of IL-1
       pattern 1, pattern 2 and/or pattern 3. In other aspect, the invention
       relates to methods for selecting a therapeutic regimen, identifying
       age-related biomarkers, monitoring the progress of age-related
       conditions and identifying therapeutics for delaying or diminishing the
       onset of aging-related conditions.
ABFR   Certains modes de realisation de l'invention concernent des methodes de
       determination de la receptivite d'un sujet a l'apparition precoce ou a
       la progression d'etats lies au vieillissement. Certains modes de
       realisation de l'invention concernent l'acces au genotype d'un sujet par
       rapport a un allele de l'interleukine-1 (IL-1) modele 1, modele 2 et/ou
       modele 3. Dans un autre mode de realisation, l'invention concerne des
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methodes de selection d'un regime therapeutique, d'identification de marqueurs biologiques lies au vieillissement, de surveillance de la progression d'etats lies au vieillissement et d'identification de therapies permettant de retarder ou de diminuer l'apparition d'etats lies au vieillissement.

L13 ANSWER 2 OF 10 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2002101015 PCTFULL ED 20030102 EW 200251
TITLE (ENGLISH): INTEGRATIVE ASSAYS FOR MONITORING MOLECULAR ASSEMBLY EVENTS
TITLE (FRENCH): TECHNIQUES D'ESSAIS INTEGRATIFS POUR LE CONTROLE D'EVENEMENTS D'ASSEMBLAGE MOLECULAIRE
INVENTOR(S): DOWER, Steven; DUFF, Gordon, W.
PATENT ASSIGNEE(S): INTERLEUKIN GENETICS, INC.
AGENT: OLESEN, James, T.
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002101015	A2	20021219

DESIGNATED STATES: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
APPLICATION INFO.: WO 2002-US18346 A 20020611
PRIORITY INFO.: US 2001-60/297,305 20010611
ABEN The invention relates to methods, compositions, and apparatus for monitoring molecular assembly events. Monitoring such molecular assembly events, in combination with other assays such as genetic screening, permits the dissection of genetic and nongenetic influences on a particular biological activity.
ABFR L'invention concerne des procedes, des compositions et un appareil destines a controler des evenements d'assemblage moleculaire. Le controle de tels evenements d'assemblage moleculaire, combine avec d'autres essais comme le depistage genetique, permet d'analyser l'existence d'influences genetiques ou autres sur une activite biologique particuliere.

L13 ANSWER 3 OF 10 USPATFULL
ACCESSION NUMBER: 2002:331268 USPATFULL
TITLE: Osteopontin knock-out mouse and methods of use thereof
INVENTOR(S): Denhardt, David T., Bridgewater, NJ, UNITED STATES
Rittling, Susan R., Kingston, NJ, UNITED STATES
Noda, Masaki, Tokyo, JAPAN
Kowalski, Aaron J., Piscataway, NJ, UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2002188962	A1	20021212
APPLICATION INFO.: US 2002-188884	A1	20020702 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-340484, filed on 30 Jun 1999, GRANTED, Pat. No. US 6414219

NUMBER	DATE
PRIORITY INFORMATION: US 1998-91200P	19980630 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DANN DORFMAN HERRELL & SKILLMAN, SUITE 720, 1601 MARKET STREET, PHILADELPHIA, PA, 19103-2307
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 1586
AB A transgenic non-human animal with alterations in the osteopontin gene

is prepared by introduction of a gene encoding an altered osteopontin protein into a host non-human animal. Methods for using transgenic mice so generated to screen for agents that effect osteopontin's cellular modulating activity are also provided.

L13 ANSWER 4 OF 10 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002633269 MEDLINE
DOCUMENT NUMBER: 22267125 PubMed ID: 12379707
TITLE: Interleukin-10 (IL-10) in experimental visceral leishmaniasis and IL-10 receptor blockade as immunotherapy.
AUTHOR: Murray Henry W; Lu Christina M; Mauze Smita; Freeman Sherry; Moreira Andre L; Kaplan Gilla; Coffman Robert L
CORPORATE SOURCE: Department of Medicine, Weill Medical College of Cornell University, New York, New York 10021, USA.. hwmurry@med.cornell.edu
CONTRACT NUMBER: AI16963 (NIAID)
AI22616 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (2002 Nov) 70 (11) 6284-93. Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20021213
Entered Medline: 20021108
AB Interleukin-10 (IL-10) is thought to promote intracellular infection, including **human** visceral leishmaniasis, by disabling Th1 cell-type responses and/or deactivating parasitized tissue macrophages. To develop a rationale for IL-10 inhibition as treatment in visceral infection, Th1 cytokine-driven responses were characterized in Leishmania donovani-infected BALB/c mice in which IL-10 was absent or overexpressed or its receptor (IL-10R) was blockaded. IL-10 **knockout** and normal mice treated prophylactically with anti-IL-10R demonstrated accelerated granuloma assembly and rapid parasite killing without untoward tissue inflammation; IL-12 and gamma interferon mRNA expression, **inducible nitric oxide synthase** reactivity, and responsiveness to antimony chemotherapy were also enhanced in **knockout** mice. In IL-10 **transgenic mice**, parasite replication was unrestrained, and except for antimony responsiveness, measured Th1 cell-dependent events were all initially impaired. Despite subsequent granuloma assembly, high-level infection persisted, and antimony-treated **transgenic mice** also relapsed. In normal mice with established infection, anti-IL-10R treatment was remarkably active, inducing near-cure by itself and synergism with antimony. IL-10's deactivating effects regulate outcome in experimental visceral leishmaniasis, and IL-10R blockade represents a potential immuno- and/or immunochemotherapeutic approach in this infection.

L13 ANSWER 5 OF 10 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002408347 IN-PROCESS
DOCUMENT NUMBER: 22152065 PubMed ID: 12162464
TITLE: Upregulation of phosphoinositide 3-kinase and protein kinase B in alveolar macrophages following ozone inhalation. role of NF-kappaB and STAT-1 in ozone-induced nitric oxide production and toxicity.
AUTHOR: Laskin Debra L; Fakhrzadeh Ladan; Heck Diane E; Gerecke Donald; Laskin Jeffrey D
CORPORATE SOURCE: Environmental and Occupational Health Sciences Institute, Rutgers University and University of Medicine and Dentistry of New Jersey, Piscataway, USA.. laskin@eohsi.rutgers.edu
CONTRACT NUMBER: ES04738 (NIEHS)
ES05022 (NIEHS)

ES06897 (NIEHS)
GM34310 (NIGMS)
HL67708 (NHLBI)

SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (2002 May-Jun) 234-235 (1-2) 91-8.
Journal code: 0364456. ISSN: 0300-8177.

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20021212

AB Inhalation of toxic doses of ozone causes lung injury and inflammation in **humans** and experimental animals. Using a rodent model of ozone toxicity, we have previously demonstrated that macrophages recruited to the lung following exposure to this oxidant contribute to the pathogenesis of tissue injury. In the present studies we analyzed potential mechanisms regulating alveolar macrophage activity following ozone inhalation and the role of inflammatory mediators in toxicity. Treatment of mice with ozone (0.8 ppm, 3 h) resulted in increased expression of **inducible nitric oxide synthase** (**iNOS**) protein and production of nitric oxide (NO) and peroxynitrite by alveolar macrophages. In contrast, these effects were not observed in macrophages from **transgenic mice** with a targeted disruption of the gene for **iNOS**, or in mice overexpressing superoxide dismutase. Moreover, ozone toxicity, as measured by bronchoalveolar lavage protein levels and nitrotyrosine staining of the lung was prevented in both of these **transgenic mouse** strains. The promoter/enhancer region of the **iNOS** gene contains binding sites for the transcription factors NF-kappaB and STAT-1 which regulate the activity of the gene. Ozone inhalation resulted in a rapid and prolonged activation of NF-kappaB in alveolar macrophages. Phosphoinositide 3-kinase (PI 3-K) and its down stream target, protein kinase B (PKB), which are known to regulate NF-kappaB activity, also increased in alveolar macrophages following ozone inhalation. These data, together with our findings that inhibitors of PI 3-K block NO production, suggest that these proteins are important in controlling expression of **iNOS**. Furthermore, the fact that macrophages from NF-kappaB p50 **knockout** mice did not generate reactive nitrogen intermediates and that these mice were protected from ozone induced toxicity demonstrate the importance of the NF-kappaB signaling pathway in lung injury. We also found that STAT-1 nuclear binding activity and STAT-1 protein expression were upregulated in macrophages from ozone treated animals. Taken together, these data suggest that biochemical signaling pathways that control the expression of genes critical for the inflammatory process play a role in ozone toxicity.

L13 ANSWER 6 OF 10 PCTFULL COPYRIGHT 2003 Univentio

ACCESSION NUMBER: 2001060408 PCTFULL ED 20020822
TITLE (ENGLISH): MICROCOMPETITON AND HUMAN DISEASE
TITLE (FRENCH): MICRO-COMPETITION ET MALADIE HUMAINE
INVENTOR(S): POLANSKY, Hanan
PATENT ASSIGNEE(S): SCI PHARMACEUTICALS, INC.; POLANSKY, Hanan
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2001060408	A2	20010823

DESIGNATED STATES: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US5314 A 20010216
PRIORITY INFO.: US 2000-60/183,184 20000217
US 2000-09/732,360 20001207

ABEN Cellular microcompetition for the transcription factor human GA binding protein (GABP) is a risk factor associated with obesity and obesity-related diseases such as osteoarthritis, atherosclerosis, obstructive sleep apnea, various cancers, and periodontitis. The invention uses this novel discovery to develop assays which determine the level of microcompetition in a cell. Other assays developed from the knowledge that microcompetition is occurring in cells are also disclosed. This novel discovery led to the development of assays which can determine the level of microcompetition in a cell and to select compounds to target this microcompetition syndrome. In addition, methods to treat a patient for microcompetition based disease are taught.

ABFR La micro-competition cellulaire pour la proteine humaine de fixation GA du facteur de transcription (GABP) est un facteur de risque associe a l'obesite et a des troubles lies a l'obesite tels que l'arthrose, l'atherosclerose, l'apnee obstructive, divers cancers et la parodontite. Cette decouverte permet de mettre au point des epreuves biologiques aux fins de la determination de l'importance de la micro-competition dans une cellule. L'invention porte egalement sur d'autres epreuves mises au point a partir de la connaissance du fait que cette micro-competition survient dans des cellules. Cette invention debouche sur la mise au point d'epreuves biologiques permettant de determiner l'importance de la micro-competition dans une cellule et de selectionner des composes permettant de cibler le syndrome de la micro-competition. L'invention concerne, de surcroit, des methodes de traitement de patients souffrant de troubles lies a la micro-competition.

L13 ANSWER 7 OF 10 USPATFULL
ACCESSION NUMBER: 2001:191334 USPATFULL
TITLE: Endothelial NOS knockout mice and methods of use
INVENTOR(S): Huang, Paul L., Boston, MA, United States
Fishman, Mark C., Newton Center, MA, United States
Moskowitz, Michael A., Belmont, MA, United States
PATENT ASSIGNEE(S): The General Hospital Corporation, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6310270	B1	20011030	
APPLICATION INFO.:	US 1997-818082		19970314	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-13525P	19960315 (60)
	US 1996-27362P	19960918 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Martin, Jill D.
ASSISTANT EXAMINER: Baker, Anne-Marie
LEGAL REPRESENTATIVE: Sterne, Kessler, Goldstein & Fox P.L.L.C.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 53 Drawing Figure(s); 24 Drawing Page(s)
LINE COUNT: 2949
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to transgenic non-human animals comprising a disrupted endothelial nitric oxide synthase gene. These animals exhibit abnormal wound-healing properties and hypertension. This invention also relates to methods of using the transgenic animals to screen for compounds having a potential therapeutic utility for vascular endothelial disorders, such as hypertension, cerebral ischemia or stroke, atherosclerosis and wound-healing activities. Moreover, this invention also relates to methods of treating a patient suffering from

hypertension and wound-healing abnormalities with the compounds identified using the transgenic animals, and methods of making the transgenic animals. A method of treating a wound using nitroglycerin is also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L13 ANSWER 8 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

ACCESSION NUMBER: 2002:112515 BIOSIS
DOCUMENT NUMBER: PREV200200112515
TITLE: **Inducible nitric oxide synthase** expression and nitrotyrosine formation in **humans** and **knockout-transgenic mice** with sickle cell disease.
AUTHOR(S): Aslan, Mutay (1); Ryan, Thomas; Townes, Tim; Baldus, Stephan; Freeman, Bruce
CORPORATE SOURCE: (1) Department of Anesthesiology, Center for Free Radical Biology and Comprehensive Sickle Cell Disease Center, University of Alabama at Birmingham, Birmingham, AL, 35233 USA
SOURCE: Free Radical Biology & Medicine, (November, 2001) Vol. 31, No. 10, pp. S67. print.
Meeting Info.: 8th Annual Meeting of the Oxygen Society Research Triangle Park, North Carolina, USA November 15-19, 2001
ISSN: 0891-5849.
DOCUMENT TYPE: Conference
LANGUAGE: English

L13 ANSWER 9 OF 10 PCTFULL COPYRIGHT 2003 Univentio

ACCESSION NUMBER: 2000060117 PCTFULL ED 20020515
TITLE (ENGLISH): PREDICTION OF RISK OF INTERSTITIAL LUNG DISEASE
TITLE (FRENCH): PREDICTION DES RISQUES DE PATHOLOGIE INTERSTITIELLE PULMONAIRE
INVENTOR(S): DUFF, Gordon, W.; DI GIOVINE, Francesco, Saverio; WHYTE, Moria
PATENT ASSIGNEE(S): INTERLEUKIN GENETICS, INC.; DUFF, Gordon, W.; DI GIOVINE, Francesco, Saverio; WHYTE, Moria
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000060117	A2	20001012
DESIGNATED STATES	AE AU BR CA CN CZ HU IL JP KR MX NO NZ PL RU SG TR US YU ZA AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 2000-US8492	A	20000331
PRIORITY INFO.:	US 1999-09/286,108		19990402

ABEN The present invention provides novel methods and kits for determining whether a subject has or is likely to develop an interstitial lung disorder such as pulmonary fibrosis; as well as methods for treating an ILD and screening assays for identifying novel ILD therapeutics.

ABFR L'invention concerne des methodes et des kits nouveaux permettant de determiner si un sujet est atteint d'une pathologie interstitielle pulmonaire ou s'il est susceptible de developper une telle pathologie, telle que la fibrose pulmonaire. L'invention concerne egalement des methodes de traitement d'une pathologie interstitielle pulmonaire et des essais de criblage pour identifier de nouvelles therapeutiques contre ces pathologies.

L13 ANSWER 10 OF 10 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 1997033989 PCTFULL ED 20020514
TITLE (ENGLISH): TRANSGENIC ANIMALS HAVING A DISRUPTED eNOS GENE AND USE THEREOF
TITLE (FRENCH): ANIMAUX TRANSGENIQUES PRESENTANT UN GENE eNOS A ACTIVITE PERTURBEE ET LEUR UTILISATION
INVENTOR(S): HUANG, Paul, L.; FISHMAN, Mark, C.; MOSKOWITZ, Michael, A.
PATENT ASSIGNEE(S): THE GENERAL HOSPITAL CORPORATION
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9733989	A1	19970918
DESIGNATED STATES	CA JP MX AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1997-US4184	A	19970314
PRIORITY INFO.:	US 1996-60/013,525		19960315
	US 1996-60/027,362		19960918

ABEN This invention relates to transgenic non-human animals comprising a disrupted endothelial nitric oxide synthase gene. These animals exhibit abnormal wound-healing properties and hypertension. This invention also relates to methods of using the transgenic animals to screen for compounds having a potential therapeutic utility for vascular endothelial disorders, such as hypertension, cerebral ischemia or stroke, atherosclerosis and wound-healing activities. Moreover, this invention also relates to methods of treating a patient suffering from hypertension and wound-healing abnormalities with the compounds identified using the transgenic animals, and methods of making the transgenic animals. A method of treating a wound using nitroglycerin is also provided.

ABFR L'invention porte sur des animaux transgeniques presentant un gene endothelial de la synthase de l'oxyde nitrique (eNOS) a activite perturbee. Ces animaux presentent une cicatrisation anormale et de l'hypertension. L'invention porte egalement sur des methodes d'utilisation desdits animaux transgeniques pour detecter certains composes presentant une utilite therapeutique potentielle vis-a-vis des troubles vasculaires endotheliaux tels que l'hypertension, l'ischemie et les attaques cerebrales, l'atherosclerose, et le processus de cicatrisation. L'invention porte de plus sur des procedes de traitement de patients souffrant d'hypertension et d'anomalies de cicatrisation par des composes identifies en utilisant des animaux transgeniques, et sur des procedes de creation d'animaux transgeniques. L'invention porte enfin sur un procede de traitement des plaies a l'aide de nitroglycerine.

=> d his

(FILE 'HOME' ENTERED AT 11:46:40 ON 03 FEB 2003)

FILE 'MEDLINE, PCTFULL, USPATFULL' ENTERED AT 11:46:56 ON 03 FEB 2003
L1 29514 S TRANSGENIC MOUSE
L2 9003 S INOS OR INDUCIBLE NITRIC OXIDE SYNTHASE OR INDUCIBLE NITRIC O

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L3            59 S L1 (S) L2
L4          1638 S (KNOCKOUT OR DEFICINET ) (S) L1
L5          1610 S HUMAN (S) L2
L6             2 S L4 (S) L5
L7             9 S L4 (L) L5
L8            59 DUP REM L3 (0 DUPLICATES REMOVED)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, PCTFULL, USPATFULL, CONFSCI,
     SCISEARCH' ENTERED AT 11:54:36 ON 03 FEB 2003
L9           244 S L3
L10            9 S L6
L11          244 S L9
L12           16 S L7
L13           10 DUP REM L10 L12 (15 DUPLICATES REMOVED)

=> dup rem l11
PROCESSING COMPLETED FOR L11
L14           86 DUP REM L11 (158 DUPLICATES REMOVED)

=> d 1-86 ibib abs

L14  ANSWER 1 OF 86  USPATFULL
ACCESSION NUMBER:        2003:23312  USPATFULL
TITLE:                   Prevention of insulin-dependent diabetes, complications
                         thereof, or allograft rejection by inhibition of
                         cyclooxygenase-2 activity
INVENTOR(S):             Tabatabaie, Tahereh, Norman, OK, UNITED STATES
                         Kotake, Yashige, Oklahoma City, OK, UNITED STATES
PATENT ASSIGNEE(S):      Oklahoma Medical Research Foundation (U.S. corporation)

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2003017148      A1   20030123
APPLICATION INFO.:       US 2001-852587     A1   20010510  (9)

                                 NUMBER         DATE
                         ------------------- --------
PRIORITY INFORMATION:    US 2000-203572P     20000511 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    Daniel S. Hodgins, HEAD, JOHNSON & KACHIGIAN, Ste.
                         3030, 204 N. Robinson, Oklahoma City, OK, 73102
NUMBER OF CLAIMS:        23
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      9 Drawing Page(s)
LINE COUNT:              1118
AB       Insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease
         believed to be caused by an inflammatory process in the pancreas leading
         to selective destruction of the .beta. cells. Inducible cyclooxygenase
         (COX-2) is expressed under inflammatory conditions and its product
         prostaglandin E.sub.2 (PGE.sub.2) is an important inflammation mediator.
         Administration of the selective COX-2 inhibitor such as, e.g., NS-398
         prevents the onset of diabetes in mice brought on by multiple low-doses
         of streptozotocin (STZ). Histological observations indicated that
         STZ-mediated destruction of .beta. cells was prevented by NS-398
         treatment. Delayed (day 3) administration of NS-398 was also protective
         in this model. These results demonstrate the critical importance of
         COX-2 activity in autoimmune destruction of .beta. cells, and point to
         the fact that COX-2 inhibition should provide a preventive therapy
         against IDDM or other autoimmune problems, including allograft
         rejection. Inhibitors of NF-.kappa.B activation may also be used to
         prevent IDDM and allograft rejection.


L14  ANSWER 2 OF 86      MEDLINE                          DUPLICATE 1
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ACCESSION NUMBER: 2003012347 MEDLINE
DOCUMENT NUMBER: 22399628 PubMed ID: 12512036
TITLE: Regulation of intestinal nuclear factor-kappaB activity and E-selectin expression during sepsis: a role for peroxynitrite.
AUTHOR: Lush Cameron W; Cepinskas Gediminas; Kvietys Peter R
CORPORATE SOURCE: Department of Physiology, Lawson Health Research Institute, University of Western Ontario, London, Ontario, Canada N6A 4G5.
SOURCE: GASTROENTEROLOGY, (2003 Jan) 124 (1) 118-28.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20030110
Last Updated on STN: 20030128
Entered Medline: 20030127

AB BACKGROUND & AIMS: During sepsis, the production of both nitric oxide and superoxide are increased. Furthermore, NO and O(2)(-) may interact to produce peroxynitrite. The major aim of the present study was to assess the relative roles of NO, O(2)(-), and ONOO- in the regulation of nuclear factor kappaB (NF-kappaB) activity and subsequent E-selectin expression during the early stages of sepsis. METHODS: Mice were administered 5 microg lipopolysaccharide (LPS) intraperitoneally, and NF-kappaB activity and E-selectin expression in the small intestine were assessed 3 hours later. RESULTS: In wild-type mice, increased levels of NF-kappaB in nuclear extracts were noted. By contrast, in both **inducible nitric oxide synthase**-deficient and transgenic Cu/Zn superoxide dismutase-overexpressing mice, NF-kappaB mobilization to the nucleus was diminished. Pretreatment with a ONOO- decomposition catalyst (5,10,15,20-tetrakis[4-sulfonatophenyl]porphyrinato iron [III] [FeTPPS]) resulted in a diminished impact of LPS on NF-kappaB activation. LPS increased vascular E-selectin expression in wild-type mice. E-selectin expression was diminished in **inducible nitric oxide synthase**-deficient mice after LPS challenge, but E-selectin expression remained elevated in both Cu/Zn superoxide dismutase **transgenic mice** and wild-type mice pretreated with FeTPPS. CONCLUSIONS: Our observations suggest that NO, O(2)(-), and ONOO- production are all important mediators in the induction of NF-kappaB activity during endotoxemia and that, in vivo, E-selectin expression on endothelium may not always be associated with whole-organ NF-kappaB activation.

L14 ANSWER 3 OF 86 PCTFULL
ACCESSION NUMBER: 2002097441 PCTFULL ED 20021217 EW 200249
TITLE (ENGLISH): MAMMALIAN DIABETES-MEDIATING PROTEINS
TITLE (FRENCH): PROTEINES DE MAMMIFERE MEDIATRICES DU DIABETE
INVENTOR(S): LARSEN, Peter, Mose; FEY, Stephen, J.; KARLSEN, Allan, E.; SPARRE, Thomas; NERUP, Jorn
PATENT ASSIGNEE(S): SYDDANSK UNIVERSITET, for all designates States except US; LARSEN, Peter, Mose, for US only; FEY, Stephen, J., for US only; KARLSEN, Allan, E., for US only; SPARRE, Thomas, for US only; NERUP, Jorn, for US only
AGENT: PLOUGMANN & VINGTOFT A/S
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002097441	A2	20021205

DESIGNATED STATES AE AG AL AM AT AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ CZ DE DE DK DK DM DZ EC EE EE ES FI FI GB GD

GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SK SL TJ TM TN TR TT TZ UA UG US
UZ VN YU ZA ZM ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM
ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI
FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA
GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-DK368 A 20020529
PRIORITY INFO.: DK 2001-PA 2001 00852 20010529
DK 2002-PA 2002 00446 20020322

ABEN Provided are mammalian secreted and non-secreted diabetes mediating proteins, including protective and deleterious diabetes-mediating proteins, as well as polynucleotides encoding same, drug screening methods for identifying a test compound capable of altering the expression of a diabetes-mediating protein, and methods of preventing or ameliorating diabetes by administering a compound capable of altering the expression of a diabetes-mediating protein.

ABFR Cette invention concerne des proteines de mammifere mediatrices du diabete secretees et non secretees, y compris des proteines mediatrices du diabete protectrices et deleteres, ainsi que des polynucleotides codants ces proteines, des methodes de criblage de medicaments servant a identifier un compose de test pouvant modifier l'expression d'une proteine mediatrice du diabete, et des methodes de prevention ou d'amelioration du diabete consistant a administrer un compose pouvant modifier l'expression d'une proteine mediatrice du diabete.

L14 ANSWER 4 OF 86 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2002080894 PCTFULL ED 20021028 EW 200242
TITLE (ENGLISH): NOVEL USE OF TYROSINE KINASE INHIBITOR
TITLE (FRENCH): NOUVELLE UTILISATION D'UN INHIBITEUR DE KINASE DE TYROSINE
INVENTOR(S): WELSH, Michael; ANNEREN, Cecilia
PATENT ASSIGNEE(S): INNOVENTUS PROJECT AB, for all designates States except US; WELSH, Michael, for US only; ANNEREN, Cecilia, for US only
AGENT: DR. LUDWIG BRANN PATENTBYRA
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2002080894	A1	20021017

DESIGNATED STATES AE AG AL AM AT AT AU AZ BA BB BG BR BY BZ CA CH CN CO
CR CU CZ CZ DE DE DK DK DM DZ EC EE EE ES FI FI GB GD
GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SK SL TJ TM TN TR TT TZ UA UG US
UZ VN YU ZA ZM ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM
ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI
FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA
GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-SE682 A 20020405
PRIORITY INFO.: SE 2001-0101230-1 20010406

ABEN The present invention relates to a novel use of a tyrosine kinase inhibitor or blocking agent. More precisely, it relates to use of an inhibitor of tyrosine kinase for production of a drug for prevention/treatment of type I diabetes mellitus, wherein the inhibitor is a GTK (BSK, IYK, FRK, RAK) tyrosine kinase. The invention also relates to use of FRK (or its equivalents) or the gene encoding the same, in an assay to screen for compounds interfering with FRK activity in pancreatic β-cells. Furthermore, the invention relates to a method of prevention/treatment of type I diabetes mellitus, comprising administration of an inhibitor against a FRK tyrosine kinase in pancreatic β-cells to type I diabetic patients.

ABFR La presente invention concerne une nouvelle utilisation d'un inhibiteur kinase de tyrosine ou d'un agent bloquant. L'invention concerne egalement l'utilisation d'un inhibiteur de kinase de tyrosine pour la production d'un medicament de prevention/traitement du diabete sucre de type I, l'inhibiteur etant une kinase de tyrosine GTK (BSK, IYK, FRK, RAK). L'invention concerne egalement l'utilisation de FRK (ou ses equivalents) ou le codage du gene lui-meme, dans un dosage pour cribler les composes interferant avec l'activite FRK dans les cellules pancreatiques β. De plus, l'invention concerne un procede de prevention/traitement du diabete sucre de type I comportant l'administration d'un inhibiteur a l'encontre d'une kinase de tyrosine FRK dans les cellules β pancreatiques de patients souffrant d'un diabete de type I.

L14 ANSWER 5 OF 86 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2002047672 PCTFULL ED 20020709 EW 200225
TITLE (ENGLISH): TREATMENT OF CYSTIC FIBROSIS
TITLE (FRENCH): TRAITEMENT DE LA MUCOVISCIDOSE
INVENTOR(S): DERETIC, Vojo, P.; POSCHET, Jens, F.; BOUCHER, J., Cliff
PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF MICHIGAN, for all designates States except US; DERETIC, Vojo, P., for US only; POSCHET, Jens, F., for US only; BOUCHER, J., Cliff, for US only
AGENT: ANDREWS, Jaen
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002047672	A2	20020620

DESIGNATED STATES AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZM ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US47764 A 20011207
PRIORITY INFO.: US 2000-60/254,712 20001211
ABEN The present invention relates to methods of treating cystic fibrosis, and in particular to exposing cystic fibrosis cells to alkalinizing agents.
ABFR La presente invention se rapporte a des methodes de traitement de la mucoviscidose et notamment a une methode consistant a exposer les cellules fibro-kystiques a des agents d'alcalinisation.

L14 ANSWER 6 OF 86 USPATFULL
ACCESSION NUMBER: 2002:252890 USPATFULL
TITLE: NON-INVASIVE EVALUATION OF PHYSIOLOGICAL RESPONSE IN A MAMMAL
INVENTOR(S): ZHANG, NING, ALAMEDA, CA, UNITED STATES
CONTAG, PAMELA R., SAN JOSE, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002138855	A1	20020926	
APPLICATION INFO.:	US 1999-464795	A1	19991216	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-112646P	19981217 (60)

	US 1999-152853P 19990908 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Gary R. Fabian, Robins & Associates, 90 Middlefield Road, Suite 200, Menlo Park, CA, 94301
NUMBER OF CLAIMS:	64
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Page(s)
LINE COUNT:	3378

AB The present invention relates to panels of reporter expression cassettes and the generation of transgenic non-human animals, wherein said reporter expression cassettes have selected control elements operable linked to reporter genes. The invention includes methods of use thereof for the identification and characterization of the effects of compounds administered to the live transgenic non-human animals.

L14 ANSWER 7 OF 86 USPATFULL

ACCESSION NUMBER:	2002:37888 USPATFULL		
TITLE:	Use of tetracycline derivatives in treating multiple sclerosis		
INVENTOR(S):	Duncan, Ian D., Madison, WI, UNITED STATES Zhang, Su-Chun, Madison, WI, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002022608	A1	20020221
APPLICATION INFO.:	US 2001-848139	A1	20010503 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2000-202138P		20000505 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	QUARLES & BRADY LLP, 411 E. WISCONSIN AVENUE, SUITE 2040, MILWAUKEE, WI, 53202-4497		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Page(s)		
LINE COUNT:	677		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating multiple sclerosis is disclosed. In one embodiment, the method comprises the step of treating a multiple sclerosis patient with a tetracycline derivative, wherein the multiple sclerosis symptoms of the patient are diminished.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 8 OF 86 MEDLINE DUPLICATE 2

ACCESSION NUMBER:	2002439300 MEDLINE
DOCUMENT NUMBER:	22162441 PubMed ID: 12032144
TITLE:	Accelerated phagocytosis of amyloid-beta by mouse and human microglia overexpressing the macrophage colony-stimulating factor receptor.
AUTHOR:	Mitrasinovic Olivera M; Murphy Greer M Jr
CORPORATE SOURCE:	Neuroscience Research Laboratories, Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, California 94305-5485, USA.
CONTRACT NUMBER:	AG17824 (NIA) MH40041 (NIMH) MH57833 (NIMH)
SOURCE:	JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Aug 16) 277 (33) 29889-96. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:	United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020829
Last Updated on STN: 20030105
Entered Medline: 20020920

AB Microglia surrounding A beta plaques in Alzheimer's disease and in the APPV717F **transgenic mouse** model of Alzheimer's disease have enhanced immunoreactivity for the macrophage colony-stimulating factor receptor (M-CSFR), encoded by the proto-oncogene c-fms. Increased expression of M-CSFR on cultured microglia results in proliferation and release of pro-inflammatory cytokines and expression of **inducible nitric-oxide synthase**. We transfected mouse BV-2 and human SV-A3 microglia to overexpress M-CSFR and examined microglial phagocytosis of fluorescein-conjugated A beta. Flow cytometry and laser confocal microscopy showed accelerated phagocytosis of A beta in mouse and human microglia because of M-CSFR overexpression that was time- and concentration-dependent. In contrast, microglial uptake of 1-microm diameter polystyrene microspheres was not enhanced by M-CSFR overexpression. Microglial uptake of A beta was blocked by cytochalasin D, which inhibits phagocytosis. M-CSFR overexpression increased the mRNA for macrophage scavenger receptor A, and fucoidan blocking of macrophage scavenger receptors inhibited uptake of A beta. M-CSFR antibody blocking experiments demonstrated that increased A beta uptake depended on the interaction of the M-CSFR with its ligand. These results suggest that overexpression of M-CSFR in APPV717F mice may prime microglia for phagocytosis of A beta after immunization.

L14 ANSWER 9 OF 86 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002402355 MEDLINE
DOCUMENT NUMBER: 22146354 PubMed ID: 12151533
TITLE: Overexpression of HGF retards disease progression and prolongs life span in a transgenic mouse model of ALS.
AUTHOR: Sun Woong; Funakoshi Hiroshi; Nakamura Toshikazu
CORPORATE SOURCE: Division of Molecular Regenerative Medicine, Course of Advanced Medicine, Osaka University Graduate School of Medicine, B-7, Osaka 565-0871, Japan.
SOURCE: JOURNAL OF NEUROSCIENCE, (2002 Aug 1) 22 (15) 6537-48. Journal code: 8102140. ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020802
Last Updated on STN: 20020904
Entered Medline: 20020903

AB Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by a progressive loss of motoneurons and degeneration of motor axons. We show that overexpression of hepatocyte growth factor (HGF) in the nervous system attenuates motoneuron death and axonal degeneration and prolongs the life span of **transgenic mice** overexpressing mutated Cu2+/Zn2+ superoxide dismutase 1. HGF prevented induction of caspase-1 and **inducible nitric oxide synthase** (**iNOS**) in motoneurons and retained the levels of the glial-specific glutamate transporter (excitatory amino acid transporter 2/glutamate transporter 1) in reactive astrocytes. We propose that HGF may be the first example of an endogenous growth factor that can alleviate the symptoms of ALS by direct neurotrophic activities on motoneurons and indirect activities on glial cells, presumably favoring a reduction in glutamatergic neurotoxicity.

L14 ANSWER 10 OF 86 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2002633269 MEDLINE

DOCUMENT NUMBER: 22267125 PubMed ID: 12379707
TITLE: Interleukin-10 (IL-10) in experimental visceral leishmaniasis and IL-10 receptor blockade as immunotherapy.
AUTHOR: Murray Henry W; Lu Christina M; Mauze Smita; Freeman Sherry; Moreira Andre L; Kaplan Gilla; Coffman Robert L
CORPORATE SOURCE: Department of Medicine, Weill Medical College of Cornell University, New York, New York 10021, USA.. hwmurry@med.cornell.edu
CONTRACT NUMBER: AI16963 (NIAID)
AI22616 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (2002 Nov) 70 (11) 6284-93. Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20021213
Entered Medline: 20021108

AB Interleukin-10 (IL-10) is thought to promote intracellular infection, including human visceral leishmaniasis, by disabling Th1 cell-type responses and/or deactivating parasitized tissue macrophages. To develop a rationale for IL-10 inhibition as treatment in visceral infection, Th1 cytokine-driven responses were characterized in Leishmania donovani-infected BALB/c mice in which IL-10 was absent or overexpressed or its receptor (IL-10R) was blockaded. IL-10 knockout and normal mice treated prophylactically with anti-IL-10R demonstrated accelerated granuloma assembly and rapid parasite killing without untoward tissue inflammation; IL-12 and gamma interferon mRNA expression, **inducible nitric oxide synthase** reactivity, and responsiveness to antimony chemotherapy were also enhanced in knockout mice. In IL-10 **transgenic mice**, parasite replication was unrestrained, and except for antimony responsiveness, measured Th1 cell-dependent events were all initially impaired. Despite subsequent granuloma assembly, high-level infection persisted, and antimony-treated **transgenic mice** also relapsed. In normal mice with established infection, anti-IL-10R treatment was remarkably active, inducing near-cure by itself and synergism with antimony. IL-10's deactivating effects regulate outcome in experimental visceral leishmaniasis, and IL-10R blockade represents a potential immuno- and/or immunochemotherapeutic approach in this infection.

L14 ANSWER 11 OF 86 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2002719205 IN-PROCESS
DOCUMENT NUMBER: 22321447 PubMed ID: 12391106
TITLE: Pulmonary hypertension in TNF-alpha-overexpressing mice is associated with decreased VEGF gene expression.
AUTHOR: Fujita Masaki; Mason Robert J; Cool Carleyne; Shannon John M; Hara Nobuyuki; Fagan Karen A
CORPORATE SOURCE: Research Institute for Disease of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582 Japan.
CONTRACT NUMBER: HL-56556 (NHLBI)
SOURCE: JOURNAL OF APPLIED PHYSIOLOGY, (2002 Dec) 93 (6) 2162-70. Journal code: 8502536. ISSN: 8750-7587.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021218
Last Updated on STN: 20021218

AB Tumor necrosis factor-alpha (TNF-alpha) **transgenic mice** have previously been found to have characteristics consistent with emphysema and severe pulmonary hypertension. Lungs demonstrated alveolar

enlargement as well as interstitial thickening due to chronic inflammation and perivascular fibrosis. In the present report, we sought to determine potential mechanisms leading to development of pulmonary hypertension in TNF-alpha **transgenic mice**. To determine whether sustained vasoconstriction was an important component of this pulmonary hypertension, nitric oxide was administered and hemodynamics were measured. Nitric oxide (25 ppm) failed to normalize right ventricular pressure in transgene-positive mice, suggesting that the pulmonary hypertension was not due to sustained vasoconstriction. Structural analysis of the pulmonary arteries found adventitial thickening and a trend toward medial hypertrophy in pulmonary arteries of transgene-positive mice, suggesting that vascular remodeling had occurred. Echocardiographic measurement of the percent fractional shortening of the left ventricle as a measurement of ventricular function in vivo revealed that left ventricular dysfunction was not contributing to pulmonary hypertension. We examined expression of genes known to be important in regulation of vascular tone and structure. Messenger RNA expression of vascular endothelial growth factor and its receptor flk-1 was reduced compared with transgene-negative littermates at all ages. Endothelial and **inducible nitric oxide synthase** mRNA levels were similar in both groups. Endothelin-1 mRNA was also decreased in TNF-alpha **transgenic mice**. Interestingly, female **transgenic mice** had decreased survival rate compared with male **transgenic mice**. We conclude that chronic overexpression of TNF-alpha is associated with decreased vascular endothelial growth factor and flk-1 gene expression, pulmonary vascular remodeling, and severe pulmonary hypertension, although the precise mechanism is unknown.

L14 ANSWER 12 OF 86 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2002111058 MEDLINE
DOCUMENT NUMBER: 21819430 PubMed ID: 11818564
TITLE: Beta-amyloid precursor protein transgenic mice that harbor diffuse A beta deposits but do not form plaques show increased ischemic vulnerability: role of inflammation.
AUTHOR: Koistinaho Milla; Kettunen Mikko I; Goldsteins Gundars; Keinanen Riitta; Salminen Antero; Ort Michael; Bures Jan; Liu David; Kauppinen Risto A; Higgins Linda S; Koistinaho Jari
CORPORATE SOURCE: A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, P.O. Box 1627, FIN-70211, Kuopio, Finland.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Feb 5) 99 (3) 1610-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020215
Last Updated on STN: 20030105
Entered Medline: 20020307

AB beta-amyloid (A beta), derived form the beta-amyloid precursor protein (APP), is important for the pathogenesis of Alzheimer's disease (AD), which is characterized by progressive decline of cognitive functions, formation of A beta plaques and neurofibrillary tangles, and loss of neurons. However, introducing a human wild-type or mutant APP gene to rodent models of AD does not result in clear neurodegeneration, suggesting that contributory factors lowering the threshold of neuronal death may be present in AD. Because brain ischemia has recently been recognized to contribute to the pathogenesis of AD, we studied the effect of focal brain ischemia in 8- and 20-month-old mice overexpressing the 751-amino acid isoform of human APP. We found that APP751 mice have higher activity of p38 mitogen-activated protein kinase (p38 MAPK) in microglia, the main immune effector cells within the brain, and increased vulnerability to

brain ischemia when compared with age-matched wild-type mice. These characteristics are associated with enhanced microglial activation and inflammation but not with altered regulation of cerebral blood flow, as assessed by MRI and laser Doppler flowmetry. Suppression of inflammation with aspirin or inhibition of p38 MAPK with a selective inhibitor, SD-282, abolishes the increased neuronal vulnerability in APP751 **transgenic mice**. SD-282 also suppresses the expression of **inducible nitric-oxide synthase** and the binding activity of activator protein 1. These findings elucidate molecular mechanisms of neuronal injury in AD and suggest that antiinflammatory compounds preventing activation of p38 MAPK in microglia may reduce neuronal vulnerability in AD.

L14 ANSWER 13 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:431946 BIOSIS
DOCUMENT NUMBER: PREV200200431946
TITLE: Regulated overexpression of nitric oxide in the lungs induces airway hyperresponsiveness in mice.
AUTHOR(S): Hjoberg, Josephine (1); Drazen, Jeffrey M. (1); Elias, Jack A.; Kobzik, Lester; Shore, Stephanie; Silverman, Eric S. (1)
CORPORATE SOURCE: (1) Pulmonary and Critical Care Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115 USA
SOURCE: FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A1148. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB To explore the role of nitric oxide (NO) in airway disease we have developed a regulatable **transgenic mouse** capable of overexpressing **inducible nitric oxide synthase** (**iNOS**) in an airway specific fashion. The **iNOS** mouse contains two transgenes: a rtTA under control of the CC10 promoter; and the mouse **iNOS** cDNA under control of a tetracycline response element. Addition of doxycycline (Dox, 0.5 mg/ml) to the drinking water increased **iNOS** RNA, protein, and immunohistochemical staining in the epithelium. Dox treatment increased exhaled NO from 8.8+-0.4 ppb to a plateau of 31.2+-2.8 ppb (n=7, $p<0.05$). Increased NO levels were sustained for at least 2 weeks and returned to baseline within 24 h after withdrawal of Dox. There were no differences between Dox treated or untreated **iNOS** mice and wild type mice in lung histology, BAL protein or BAL cell count. However, measuring airway responsiveness using whole body plethysmography showed that **iNOS** mice treated with Dox were hyperresponsive to methacholine (MCh). Following a PBS baseline, the mice were challenged with increasing concentrations of MCh. Before Dox treatment there was no difference in responsiveness to MCh between **iNOS** treated or untreated or wild type mice. After one day of Dox treatment the MCh dose producing 300% PBS Penh was 13+-1 mg/ml, compared with 22+-3 without Dox (n=6, $p<0.05$). These data indicate that increased levels of NO in the airways can induce airway hyperresponsiveness in the absence of inflammation.

L14 ANSWER 14 OF 86 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2002635731 MEDLINE
DOCUMENT NUMBER: 22282060 PubMed ID: 12392781
TITLE: APOE and the regulation of microglial nitric oxide production: a link between genetic risk and oxidative stress.
AUTHOR: Colton Carol A; Brown Candice M; Cook Danielle; Needham Leila K; Xu Qing; Czapiga Meggan; Saunders Ann M; Schmechel Donald E; Rasheed Karima; Vitek Michael P
CORPORATE SOURCE: Division of Neurology, Duke University Medical Center, Box

2900, Bryan Research Building, Durham, NC 27710, USA..
glia01@aol.com
SOURCE: NEUROBIOLOGY OF AGING, (2002 Sep-Oct) 23 (5) 777-85.
Journal code: 8100437. ISSN: 0197-4580.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20030111
Entered Medline: 20030110

AB The mechanism linking the APOE4 gene with increased susceptibility for Alzheimer's disease (AD) and poorer outcomes following closed head injury and stroke is unknown. One potential link is activation of the innate immune system in the CNS. Our previously published data demonstrated that apolipoprotein E regulates production of nitric oxide, a critical cytoactive factor released by immune active macrophages. To determine if immune regulation is different in the presence of apolipoprotein E4 compared to apolipoprotein E3, we have measured NO production by peritoneal and CNS macrophages (microglia) cultured from **transgenic mice** that only express the human apoE4 or apoE3 protein isoform. Significantly more NO was produced in APOE4 mice compared to APOE3 **transgenic mice** that only express human apoE3 protein. Similarly, monocyte derived macrophages from humans carrying APOE4 gene alleles also produce significantly greater NO than those individuals with APOE3. The mechanism for this isoform-specific difference in NO production is not known and multiple sites in the NO production pathway may be affected. Expression of **inducible nitric oxide synthase** (**iNOS**) mRNA and protein are not significantly different between the APOE3 and APOE4 mice, suggesting that induction of **iNOS** is not a primary cause of the increased NO production in APOE4 animals. One alternative regulatory mechanism that demonstrates isoform specificity is arginine transport, which is greater in microglia from APOE4 **transgenic mice** compared to microglia from APOE3 mice. Increased transport is consistent with an increased production of NO and may reflect a direct or indirect effect of the APOE genotype on microglial arginine uptake and microglial activation in general. Overall, greater NO production in APOE4 carriers where characteristically high levels of oxidative/nitrosative stress are found in diseases such as AD provides a mechanism that potentially explains the genetic association between APOE4 and human diseases.

L14 ANSWER 15 OF 86 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2002183257 MEDLINE
DOCUMENT NUMBER: 21898393 PubMed ID: 11901182
TITLE: Cardiomyocyte overexpression of iNOS in mice results in peroxynitrite generation, heart block, and sudden death.
AUTHOR: Mungrue Imran N; Gros Robert; You Xiaomang; Pirani Asif; Azad Azar; Csont Tamas; Schulz Richard; Butany Jagdish; Stewart Duncan J; Husain Mansoor
CORPORATE SOURCE: Heart and Stroke Richard Lewar Centre of Excellence, University of Toronto, Toronto, Ontario, Canada.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (2002 Mar) 109 (6) 735-43.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020419

Entered Medline: 20020418

AB Increased **inducible nitric oxide synthase** (**iNOS**) expression is a component of the immune response and has been demonstrated in cardiomyocytes in septic shock, myocarditis, transplant rejection, ischemia, and dilated cardiomyopathy. To explore whether the consequences of such expression are adaptive or pathogenic, we have generated a **transgenic mouse** model conditionally targeting the expression of a human **iNOS** cDNA to myocardium. Chronic cardiac-specific upregulation of **iNOS** in **transgenic mice** led to increased production of peroxynitrite. This was associated with a mild inflammatory cell infiltrate, cardiac fibrosis, hypertrophy, and dilatation. While **iNOS**-overexpressing mice infrequently developed overt heart failure, they displayed a high incidence of sudden cardiac death due to bradyarrhythmia. This dramatic cardiac phenotype was rescued by specific attenuation of transgene activity. These data implicate cardiomyocyte **iNOS** overexpression as sufficient to cause cardiomyopathy, bradyarrhythmia, and sudden cardiac death.

L14 ANSWER 16 OF 86 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2002424752 MEDLINE
DOCUMENT NUMBER: 22169256 PubMed ID: 12181430
TITLE: Blockade of nitric-oxide synthase reduces choroidal neovascularization.
AUTHOR: Ando Akira; Yang Amy; Nambu Hiroyuki; Campochiaro Peter A
CORPORATE SOURCE: Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287-9277, USA.
CONTRACT NUMBER: EY05951 (NEI)
EY12609 (NEI)
P30-EY1765 (NEI)
SOURCE: MOLECULAR PHARMACOLOGY, (2002 Sep) 62 (3) 539-44.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020816
Last Updated on STN: 20020906
Entered Medline: 20020905

AB Nitric oxide (NO) promotes retinal and choroidal neovascularization, although different isoforms of nitric-oxide synthetase (NOS) are critical in each. Deficiency of endothelial NOS (eNOS) suppresses retinal but not choroidal neovascularization, whereas deficiency of neuronal NOS (nNOS) or inducible NOS (**iNOS**) suppresses choroidal, but not retinal neovascularization. In this study, we investigated the effect of N(G)-monomethyl-L-arginine (L-NMMA), a nonspecific NOS inhibitor, in three models of ocular neovascularization. Oral administration of L-NMMA caused significant inhibition of choroidal neovascularization in mice with laser-induced rupture of Bruch's membrane and significantly inhibited subretinal neovascularization in **transgenic mice** with expression of vascular endothelial growth factor (VEGF) in photoreceptors (rho/VEGF mice) but did not inhibit retinal neovascularization in mice with ischemic retinopathy. By extensive mating among mice deficient in NOS isoforms, triple homozygous mutant mice deficient in all three NOS isoforms were produced. These mice had marked suppression of choroidal neovascularization at sites of rupture of Bruch's membrane and near-complete suppression of subretinal neovascularization in rho/VEGF mice but showed no difference in ischemia-induced retinal neovascularization compared with wild-type mice. These data indicate that NO is an important stimulator of choroidal neovascularization and that reduction of NO by pharmacologic or genetic means is a good treatment strategy. However, the situation is more complex for ischemia-induced retinal neovascularization for which NO produced in endothelial cells by eNOS is stimulatory, but NO produced in other retinal cells by

iNOS and/or nNOS is inhibitory. Selective inhibitors of eNOS may be needed for treatment of retinal neovascularization.

L14 ANSWER 17 OF 86 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2002136065 MEDLINE
DOCUMENT NUMBER: 21685816 PubMed ID: 11827697
TITLE: TNFalpha decreases alphaMHC expression by a NO mediated pathway: role of E-box transcription factors for cardiomyocyte specific gene regulation.
AUTHOR: Hilfiker-Kleiner Denise; Hilfiker Andres; Schieffer Bernhard; Engel David; Mann Douglas L; Wollert Kai C; Drexler Helmut
CORPORATE SOURCE: Department of Cardiology and Angiology, Medizinische Hochschule Hannover, Carl-Neuberg Strasse 1, 30625 Hannover, Germany.
SOURCE: CARDIOVASCULAR RESEARCH, (2002 Feb 1) 53 (2) 460-9. Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020302
Last Updated on STN: 20020312
Entered Medline: 20020311

AB OBJECTIVE: Tumor necrosis factor alpha(TNFalpha) is thought to play a key role in the pathogenesis of cardiac failure. In the myocardium, TNFalpha enhances the expression of **inducible nitric oxide synthase** (**iNOS**). Nitric oxide (NO) has been shown to affect beta-agonist-dependent cardiac contractility and relaxation. It is not clear, however, whether TNFalpha mediated NO release has sustained cardiac effects, by altering expression of cardiomyocyte specific genes such as alpha-myosin heavy chain (alphaMHC). METHODS: Neonatal rat ventricular cardiomyocytes (CM) were stimulated with TNFalpha and/or the NOS inhibitor nitro-L-arginine (L-NNA). Protein binding to the E-box enhancer element in the alphaMHC promoter was evaluated by electrophoretic mobility shift assay (EMSA) and transcriptional activity of the E-box consensus motif was determined by luciferase assay. mRNA levels of the endogenous alphaMHC gene were assessed by RT-PCR. In vivo studies were performed in **transgenic mice** with cardiac specific over-expression of TNFalpha. Results: CM treated with TNFalpha exhibited decreased levels of alphaMHC transcripts (69 +/- 8% of control), the effect of TNFalpha was reversed by L-NNA (94 +/- 14% of control). As shown by EMSA, TNFalpha reduced protein binding to the alphaMHC E-box enhancer motif via NO dependent pathways. Addition of the NO-donor sodium nitroprusside (SNP) to CM nuclear extracts dose dependently disrupted protein binding to the alphaMHC E-box. Furthermore, exposure of CM to TNFalpha or SNP decreased transcription from an E-box luciferase-reporter construct (TNFalpha: 74 +/- 12%; SNP 250 microM: 72 +/- 10%; SNP 500 microM: 66 +/- 11% of control). In myocardial tissue of TNFalpha **transgenic mice**, increased nitrotyrosine staining, decreased protein binding to the alphaMHC E-box motif and reduced expression of alphaMHC (62 +/- 26%) were observed. CONCLUSIONS: The present study shows that TNFalpha reduces alphaMHC transcript levels in cardiomyocytes. Our data obtained in cultured CM and in TNFalpha **transgenic mice** support the notion that TNFalpha exerts these effects by NO and E-box dependent mechanisms in vitro and possibly in vivo.

L14 ANSWER 18 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:363326 BIOSIS
DOCUMENT NUMBER: PREV200200363326
TITLE: Cardiac specific overexpression of **iNOS** in **transgenic mice** attenuates beta-adrenergic stimulation in vivo.

AUTHOR(S): Molojavyi, A. (1); Heger, J. (1); Schrader, J. (1); Goedecke, A. (1)
CORPORATE SOURCE: (1) Institut fuer Herz- und Kreislaufphysiologie, Heinrich-Heine-Universitaet, Universitaetsstr. 1, 40225, Duesseldorf Germany
SOURCE: Pfluegers Archiv European Journal of Physiology, (March, 2002) Vol. 443, No. Supplement 1, pp. S345. http://link.springer.de/link/service/journals/00424/. print.
Meeting Info.: 81st Annual Joint Meeting of the Physiological Society, the Scandinavian Physiological Society and the German Physiological Society Tuebingen, Germany March 15-19, 2002
ISSN: 0031-6768.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 19 OF 86 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2002132496 MEDLINE
DOCUMENT NUMBER: 21671074 PubMed ID: 11812737
TITLE: Interleukin-1 plus gamma-interferon-induced pancreatic beta-cell dysfunction is mediated by beta-cell nitric oxide production.
AUTHOR: Thomas Helen E; Darwiche Rima; Corbett John A; Kay Thomas W H
CORPORATE SOURCE: Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Melbourne, Victoria, Australia.
CONTRACT NUMBER: AI44458 (NIAID)
DK52194 (NIDDK)
SOURCE: DIABETES, (2002 Feb) 51 (2) 311-6.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020301
Last Updated on STN: 20020317
Entered Medline: 20020315

AB Cytokines have been implicated in pancreatic beta-cell destruction leading to type 1 diabetes. In vitro, a combination of gamma-interferon (IFN-gamma) and interleukin-1 (IL-1) stimulate **inducible nitric oxide synthase** (**iNOS**) expression in islets, and the resulting increased production of nitric oxide (NO) causes islet cell destruction. Islets contain macrophages, ductal cells, and endothelial cells that, when activated, may mediate islet cell damage by producing either NO themselves or cytokines that then stimulate NO production by beta-cells. The aim of this study was to determine whether beta-cell damage mediated by cytokine-induced NO production is dependent on beta-cell production of NO, or whether NO produced by other cells in the islet is capable of destroying beta-cells. To address this aim, we used **transgenic mice** expressing a dominant-negative IFN-gamma receptor in beta-cells (RIP-Delta(gamma)R). RIP-Delta(gamma)R islets are resistant to IL-1 + IFN-gamma-induced inhibition of insulin secretion and DNA damage, indicating that beta-cell IFN-gamma responsiveness is required for IL-1 + IFN-gamma-mediated beta-cell damage. Although islets isolated from RIP-Delta(gamma)R mice are resistant to functional damage, these islets produce NO in response to IL-1 + IFN-gamma, but at a lower concentration than that produced by wild-type islets. beta-Cells appear to be the primary cellular source of IL-1 + IFN-gamma-induced **iNOS** expression in wild-type islets. In contrast, IL-1 + IFN-gamma fail to stimulate **iNOS** expression by insulin-expressing cells in islets isolated from RIP-DeltagammaR mice. IL-1 + IFN-gamma-induced expression of **iNOS** was detected in non-beta-cells in both wild-type and

RIP-DeltagammaR islets. These findings support the hypothesis that NO must be produced by beta-cells to induce damage.

L14 ANSWER 20 OF 86 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 2002213743 MEDLINE
DOCUMENT NUMBER: 21946645 PubMed ID: 11950169
TITLE: Renal pathology in hemizygous sickle cell mice.
AUTHOR: Diwan B A; Gladwin M T; Noguchi C T; Ward J M; Fitzhugh A L; Buzard G S
CORPORATE SOURCE: National Cancer Institute at Frederick, Frederick, MD 21702, USA.
SOURCE: TOXICOLOGIC PATHOLOGY, (2002 Mar-Apr) 30 (2) 254-62.
Journal code: 7905907. ISSN: 0192-6233.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020413
Last Updated on STN: 20020426
Entered Medline: 20020425

AB **Transgenic mice** have been developed that express exclusively human sickle cell beta hemoglobin and have major pathological features found in humans with sickle cell disease. These mice provide a unique opportunity to investigate the fundamental mechanisms of this disease and to design new strategies to correct the associated genetic defect(s). We found that in breeding males expressing only adult human alpha-globin and sickle beta-globin (homozygous SS mice) with females containing these transgenes plus one copy of the mouse beta-globin gene (hemizygous SS mice) greater than expected numbers of hemizygous offspring were produced than homozygous mice (carrying no mouse beta-globin gene). These hemizygous mice, expressing the human alpha and sickle beta(s) transgenes in combination with mouse beta+/-, were used for our preliminary studies of their renal pathology. No kidney lesions were found in the control (129/Sv) mice, whereas about 50% of the hemizygous SS mice showed mild-to-severe kidney lesions, including glomerulonephritis, cystic atypical hyperplastic tubules, and general nephropathy. Kidneys of some hemizygous mice were normal or showed minimal nephropathy, yet those of the susceptible phenotype developed a mild-to-more-severe form of renal lesions. The tubular epithelium of kidneys of hemizygous mice of the more affected phenotype exhibited increased expression of **inducible nitric oxide synthase** with an increased 3-nitrotyrosine in close proximity. There was also a stronger immunostaining for vascular cell adhesion molecule-1 in the interstitial capillary cells as well as the tubular epithelial cells of the renal cortex, compared with normal control mice. The occurrence of a high incidence of renal abnormalities in our hemizygous SS mice suggests that these mice may provide a suitable model to study the pathogenesis of nephropathy resulting from altered blood flow and/or insufficient oxygen delivery.

L14 ANSWER 21 OF 86 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 2002102845 MEDLINE
DOCUMENT NUMBER: 21823959 PubMed ID: 11835189
TITLE: Metallothionein 1+2 protect the CNS during neuroglial degeneration induced by 6-aminonicotinamide.
AUTHOR: Penkowa Milena; Giralt Mercedes; Camats Jordi; Hidalgo Juan
CORPORATE SOURCE: Institute of Medical Anatomy, The Panum Institute, University of Copenhagen, DK-2200, Copenhagen, Denmark.
SOURCE: JOURNAL OF COMPARATIVE NEUROLOGY, (2002 Mar 5) 444 (2) 174-89.
Journal code: 0406041. ISSN: 0021-9967.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020209
Last Updated on STN: 20020314
Entered Medline: 20020313

AB 6-Aminonicotinamide (6-AN) is a niacin antagonist, which leads to degeneration of gray matter astrocytes. Metallothionein 1+2 (MT-1+2) are neuroprotective factors in the central nervous system (CNS), and to determine the roles for MT after 6-AN, we have examined **transgenic mice** overexpressing MT-1 (TgMTI* mice) after an i.p. injection with 6-AN. In control mice injected with 6-AN, astrocytes in specific gray matter areas of the brainstem showed degeneration. Reactive astrocytes surrounded the degenerated areas, which were heavily infiltrated by macrophages and T lymphocytes. MT-1+2 expression was significantly decreased in the damaged brainstem areas, but it increased in reactive astrocytes surrounding these areas and also in infiltrating macrophages. The levels of oxidative stress, as determined by immunoreactivity for **inducible nitric-oxide synthase** (**iNOS**), malondialdehyde (MDA), and nitrotyrosine (NITT), and the number of terminal deoxynucleotidyl transferase [TdT]-mediated deoxyuridine triphosphate [dUTP]-digoxigenin nick end labeling-positive (TUNEL+), caspase-3+ apoptotic cells were significantly increased in the brainstem of normal mice after 6-AN. In the TgMTI* mice, the 6-AN-induced tissue damage was decreased in comparison to control mice, and they showed significantly reduced numbers of recruited macrophages and T lymphocytes, and a drastic reduction of oxidative stress and apoptotic cell death. In addition, the accompanying reactive astrogliosis was increased in the **transgenic mice**. To further study the potential protective role of MT, we administered intraperitoneally Zn-MT-2 to 6-AN-injected normal mice and found essentially the same results as those obtained in TgMTI* mice. Thus, we hereby report that endogenous MT-1 overexpression and exogenous MT-2 treatment have significant neuroprotective roles during CNS pathological conditions.

L14 ANSWER 22 OF 86 CAPLUS
ACCESSION NUMBER: 2002:879371 CAPLUS
TITLE: The role of nitric oxide in bacterial meningitis
AUTHOR(S): Winkler, F.; Koedel, U.; Pfister, H.-W.
CORPORATE SOURCE: Department of Neurology, University of Munich, Germany
SOURCE: Recent Research Developments in Immunology (2002), 4(Pt. 1), 159-172
CODEN: RRDIB8
PUBLISHER: Research Signpost
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the brain, nitric oxide (NO) can be produced by the NO synthase (NOS) isoforms: endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS). Whereas eNOS and nNOS are expressed constitutively in adult brain and regulate major physiol. functions including vascular hemostasis and neurotransmission, iNOS is absent in strictly resting cells and is strongly induced by cytokines and other immunol. stimuli. NO prodn. in the CNS was found to increase during bacterial meningitis, both in patients and in animal models of the disease. However, the source of NO and its role in the pathogenesis of bacterial meningitis have been a matter of discussion: Contradictory results ranging from amelioration to deterioration of CNS complications and brain damage have been reported after the administration of different pharmacol. NOS inhibitors in exptl. bacterial meningitis. Not only iNOS, but also eNOS are upregulated in pneumococcal meningitis. Using **transgenic mice** deficient in eNOS and **iNOS**, it was demonstrated that both isoforms exert opposite pathophysiol. effects in the disease. Whereas eNOS-deficient mice showed aggravated CNS complications and inflammation compared with wild-type mice after pneumococcal infection, iNOS-deficient mice revealed reduced disruption of the blood-brain barrier (BBB) and

reduced expression of proinflammatory cytokines and chemokines. Staining for L-nitrotyrosin, a marker for peroxynitrite formation that contributes to BBB disruption, was increased in infected eNOS-deficient mice and abolished in iNOS-deficient mice. The opposite effects of different NOS isoforms on inflammation and cerebral complications in bacterial meningitis probably depend on the site of isoform expression, the amt. of NO prodn., and the subsequent chem. NO reactions in a specific environment (peroxynitrite formation or S-nitrosylation). Therefore, eNOS inhibition has to be prevented in this disease, whereas iNOS or peroxynitrite inhibition could be a promising target of an adjunctive therapeutic approach.

REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 23 OF 86 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 2002186386 MEDLINE
DOCUMENT NUMBER: 21917847 PubMed ID: 11920687
TITLE: Nitric oxide is proangiogenic in the retina and choroid.
AUTHOR: Ando Akira; Yang Amy; Mori Keisuke; Yamada Haruhiko; Yamada Eri; Takahashi Kyoichi; Saikia Jina; Kim Min; Melia Michele; Fishman Mark; Huang Paul; Campochiaro Peter A
CORPORATE SOURCE: Department of Ophthalmology, The Johns Hopkins University School of Medicine, Maumenee, N. Wolfe Street, Baltimore, Maryland 21287-9277, USA.
CONTRACT NUMBER: EY05951 (NEI)
EY12609 (NEI)
P30EY1765 (NEI)
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (2002 Apr) 191 (1) 116-24. Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020416
Entered Medline: 20020415

AB Nitric oxide (NO) has been shown to have proangiogenic or antiangiogenic effects depending upon the setting. In this study, we used mice with targeted deletion of one of the three isoforms of nitric oxide synthase (NOS) to investigate the effects of NO in ocular neovascularization. In **transgenic mice** with increased expression of vascular endothelial growth factor (VEGF) in photoreceptors, deficiency of any of the three isoforms caused a significant decrease in subretinal neovascularization, but no alteration of VEGF expression. In mice with laser-induced rupture of Bruch's membrane, deficiency of inducible NOS (**iNOS**) or neuronal NOS (nNOS), but not endothelial NOS (eNOS), caused a significant decrease in choroidal neovascularization. In mice with oxygen-induced ischemic retinopathy, deficiency of eNOS, but not **iNOS** or nNOS caused a significant decrease in retinal neovascularization and decreased expression of VEGF. These data suggest that NO contributes to both retinal and choroidal neovascularization and that different isoforms of NOS are involved in different settings and different disease processes. A broad spectrum NOS inhibitor may have therapeutic potential for treatment of both retinal and choroidal neovascularization.

L14 ANSWER 24 OF 86 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 2002408347 IN-PROCESS
DOCUMENT NUMBER: 22152065 PubMed ID: 12162464
TITLE: Upregulation of phosphoinositide 3-kinase and protein kinase B in alveolar macrophages following ozone inhalation. role of NF-kappaB and STAT-1 in ozone-induced nitric oxide production and toxicity.

AUTHOR: Laskin Debra L; Fakhrzadeh Ladan; Heck Diane E; Gerecke Donald; Laskin Jeffrey D
CORPORATE SOURCE: Environmental and Occupational Health Sciences Institute, Rutgers University and University of Medicine and Dentistry of New Jersey, Piscataway, USA.. laskin@eohsi.rutgers.edu
CONTRACT NUMBER: ES04738 (NIEHS)
ES05022 (NIEHS)
ES06897 (NIEHS)
GM34310 (NIGMS)
HL67708 (NHLBI)
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (2002 May-Jun) 234-235 (1-2) 91-8.
Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20021212

AB Inhalation of toxic doses of ozone causes lung injury and inflammation in humans and experimental animals. Using a rodent model of ozone toxicity, we have previously demonstrated that macrophages recruited to the lung following exposure to this oxidant contribute to the pathogenesis of tissue injury. In the present studies we analyzed potential mechanisms regulating alveolar macrophage activity following ozone inhalation and the role of inflammatory mediators in toxicity. Treatment of mice with ozone (0.8 ppm, 3 h) resulted in increased expression of **inducible nitric oxide synthase** (**iNOS**) protein and production of nitric oxide (NO) and peroxynitrite by alveolar macrophages. In contrast, these effects were not observed in macrophages from **transgenic mice** with a targeted disruption of the gene for **iNOS**, or in mice overexpressing superoxide dismutase. Moreover, ozone toxicity, as measured by bronchoalveolar lavage protein levels and nitrotyrosine staining of the lung was prevented in both of these **transgenic mouse** strains. The promoter/enhancer region of the **iNOS** gene contains binding sites for the transcription factors NF-kappaB and STAT-1 which regulate the activity of the gene. Ozone inhalation resulted in a rapid and prolonged activation of NF-kappaB in alveolar macrophages. Phosphoinositide 3-kinase (PI 3-K) and its down stream target, protein kinase B (PKB), which are known to regulate NF-kappaB activity, also increased in alveolar macrophages following ozone inhalation. These data, together with our findings that inhibitors of PI 3-K block NO production, suggest that these proteins are important in controlling expression of **iNOS**. Furthermore, the fact that macrophages from NF-kappaB p50 knockout mice did not generate reactive nitrogen intermediates and that these mice were protected from ozone induced toxicity demonstrate the importance of the NF-kappaB signaling pathway in lung injury. We also found that STAT-1 nuclear binding activity and STAT-1 protein expression were upregulated in macrophages from ozone treated animals. Taken together, these data suggest that biochemical signaling pathways that control the expression of genes critical for the inflammatory process play a role in ozone toxicity.

L14 ANSWER 25 OF 86 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 2002280172 MEDLINE
DOCUMENT NUMBER: 22015347 PubMed ID: 12020853
TITLE: Altered neuronal nitric oxide synthase expression contributes to disease progression in Huntington's disease transgenic mice.
AUTHOR: Deckel A Wallace; Tang Vinsee; Nuttal Diane; Gary Keith; Elder Robert
CORPORATE SOURCE: Department of Psychiatry, University of Connecticut Health Center, Mail Code 2103, 263 Farmington Avenue, Farmington, CT 06030-2103, USA.. deckel@psychiatry.uchc.edu
SOURCE: BRAIN RESEARCH, (2002 Jun 7) 939 (1-2) 76-86.

Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020522
Last Updated on STN: 20020829
Entered Medline: 20020828

AB Reduced neuronal NOS (nNOS) expression and biochemical activity was found in the striatum (P<0.05) and cerebellum P<0.05) of late-stage R6/1 Huntington's disease (HD) mice. The changes in NOS biochemical activity correlated with body weight (P<0.001), abnormal clasping (P<0.05) and motor functioning (P<0.05) scores. HD **transgenic mice** missing both copies of the nNOS gene showed accelerated disease progression relative to HD **transgenic mice** wildtype or heterozygous for the nNOS gene. On the other hand, mice with one copy of the nNOS gene had delayed onset of their HD-related symptoms relative to HD **transgenic mice** wildtype for nNOS. Administration of an **iNOS** inhibitor had no effect on behavioral progression. The effects of nNOS genotype on behavior may be related to abnormal expression of nNOS during development, which was increased relative to controls in R6/2 mice 3 weeks of age (presymptomatic), but decreased in R6/2 mice relative to controls at 6 (around the time of symptom onset) and 11 (late-stage disease) weeks of age. Finally, protein expression of calmodulin kinase II and IV, both of which are regulators of nNOS transcription and activation, had a pattern of increased expression early in development, and decreased expression late in development, similar to that seen for nNOS. These findings indicate that nNOS activity is altered in a complex manner in HD **transgenic mice** and suggest that these abnormalities occur in the setting of a more global disturbance of calcium-regulated proteins.

L14 ANSWER 26 OF 86 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 2002635980 MEDLINE
DOCUMENT NUMBER: 22282379 PubMed ID: 12392966
TITLE: Reduced hepatotoxicity of acetaminophen in mice lacking inducible nitric oxide synthase: potential role of tumor necrosis factor-alpha and interleukin-10.
AUTHOR: Gardner Carol R; Laskin Jeffrey D; Dambach Donna M; Sacco Michael; Durham Stephen K; Bruno Mary K; Cohen Steven D; Gordon Marion K; Gerecke Donald R; Zhou Peihong; Laskin Debra L
CORPORATE SOURCE: Environmental and Occupational Health Sciences Institute, Rutgers University, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway 08854, USA.
CONTRACT NUMBER: ES04738 (NIEHS)
ES05022 (NIEHS)
ES06897 (NIEHS)
ES07163 (NIEHS)
EY09056 (NEI)
GM34310 (NIGMS)
SOURCE: TOXICOLOGY AND APPLIED PHARMACOLOGY, (2002 Oct 1) 184 (1) 27-36.
Journal code: 0416575. ISSN: 0041-008X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20021213
Entered Medline: 20021115

AB Macrophage-derived inflammatory mediators have been implicated in tissue

injury induced by a number of hepatotoxicants. In the present studies, we used **transgenic mice** with a targeted disruption of the gene for **inducible nitric oxide synthase** (NOS II) to analyze the role of nitric oxide in inflammatory mediator production in the liver and in tissue injury induced by acetaminophen. Treatment of wild-type mice with acetaminophen (300 mg/kg) resulted in centrilobular hepatic necrosis, which was evident within 3 h and reached a maximum at 18 h. This was correlated with NOS II expression and nitrotyrosine staining of the liver, which was most prominent after 6 h. Expression of mRNA for tumor necrosis factor-alpha (TNF-alpha), interleukin-10 (IL-10), matrix metalloproteinase-9, and connective tissue growth factor (CTGF) also increased in the liver following acetaminophen treatment of wild-type mice. NOS II knockout mice were found to be less sensitive to the hepatotoxic effects of acetaminophen than wild-type mice. This did not appear to be due to differences in acetaminophen-induced glutathione depletion or adduct formation. In NOS II knockout mice treated with acetaminophen, hepatic expression of TNF-alpha, as well as CTGF, was significantly increased compared to wild-type mice. In contrast, IL-10 expression was reduced. These data demonstrate that nitric oxide is important in hepatotoxicity induced by acetaminophen. Moreover, some of its effects may be mediated by altering production of pro- and antiinflammatory cytokines and proteins important in tissue repair.

L14 ANSWER 27 OF 86 PCTFULL COPYRIGHT 2003 Univentio

ACCESSION NUMBER: 2001085175 PCTFULL ED 20020826

TITLE (ENGLISH): PREVENTION OF INSULIN-DEPENDENT DIABETES, COMPLICATIONS THEREOF, OR ALLOGRAFT REJECTION BY INHIBITION OF CYCLOOXYGENASE-2 ACTIVITY

TITLE (FRENCH): PREVENTION DU DIABETE INSULINO-DEPENDANT, DES COMPLICATIONS, OU DU REJET DE GREFFE ALLOGENIQUE PAR INHIBITION DE L'ACTIVITE DE LA CYCLOOXYGENASE DE TYPE 2

INVENTOR(S): TABATABAIE, Tahereh; KOTAKE, Yashige

PATENT ASSIGNEE(S): OKLAHOMA MEDICAL RESEARCH FOUNDATION

DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2001085175	A2	20011115

DESIGNATED STATES: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US15174 A 20010510

PRIORITY INFO.: US 2000-60/203,572 20000511

ABEN Insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease believed to be caused by an inflammatory process in the pancreas leading to selective destruction of the β cells. Inducible cyclooxygenase (COX-2) is expressed under inflammatory conditions and its product prostaglandin E2(PGE2) is an important inflammation mediator. Administration of the selective COX-2 inhibitor such as, e.g., NS-398 prevents the onset of diabetes in mice brought on by multiple low-doses of streptozotocin (STZ). Histological observations indicated that STZ-mediated destruction of β cells was prevented by NS-398 treatment. Delayed (day 3) administration of NS-398 was also protective in this model. These results demonstrate the critical importance of COX-2 activity in autoimmune destruction of β cells, and point to the fact that COX-2 inhibition should provide a preventive therapy against IDDM or other autoimmune problems, including allograft rejection. Inhibitors of NF-&kgr;B activation may also be used to prevent IDDM and allograft rejection.

ABFR Le diabete insulino-dependant (DID) est une maladie auto-immune qui semble etre provoquee par un processus inflammatoire dans le pancreas conduisant a une destruction selective des cellules β. La cyclooxygenase inductible (COX-2) est exprimee dans des etats inflammatoires et son produit, la prostaglandine E2(PGE2), est un mediateur important de l'inflammation. L'administration de l'inhibiteur selectif de COX-2, tel que, par exemple, NS-398, permet de prevenir l'apparition du diabete chez la souris induit par des doses faibles multiples de streptozotocine (STZ). Des observations histologiques indiquent que le traitement a l'aide de NS-398 permet de prevenir la destruction des cellules βinduite par la streptozotocine. L'administration reportee (jour 3) de NS-398 constitue egalement un element de protection dans ce modele. Ces resultats demontrent l'importance decisive de l'activite de COX-2 dans la destruction auto-immune des cellules β et permet d'indiquer que l'inhibition de COX-2 devrait constituer une therapie preventive contre le DID ou d'autres problemes auto-immuns, y compris le rejet de greffe allogenique. Les inhibiteurs de l'activation de NF-&kgr;B peuvent egalement etre utilises pour prevenir le DID et le rejet de greffe allogenique.

L14 ANSWER 28 OF 86 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 2001387208 MEDLINE
DOCUMENT NUMBER: 21334774 PubMed ID: 11441215
TITLE: Transgenic CuZn-superoxide dismutase inhibits NO synthase induction in experimental subarachnoid hemorrhage.
AUTHOR: Saito A; Kamii H; Kato I; Takasawa S; Kondo T; Chan P H; Okamoto H; Yoshimoto T
CORPORATE SOURCE: Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan.. atsushi@nsg.med.tohoku.ac.jp
SOURCE: STROKE, (2001 Jul) 32 (7) 1652-7.
Journal code: 0235266. ISSN: 1524-4628.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010827
Entered Medline: 20010823

AB BACKGROUND AND PURPOSE: The expression of inducible NO synthase (**iNOS**) after experimental subarachnoid hemorrhage (SAH) has been postulated to play a critical role in the pathogenesis of SAH and subsequent cerebral vasospasm. The inhibitory effect of CuZn-superoxide dismutase (CuZn-SOD) on the induction of **iNOS** after SAH was examined by using **transgenic mice** overexpressing CuZn-SOD. METHODS: SOD-**transgenic mice** and nontransgenic littermates were subjected to SAH by endovascular perforation of the left anterior cerebral artery. The **iNOS** mRNA expression after SAH was determined by reverse transcription-polymerase chain reaction, and the distribution of **iNOS**-positive cells was immunohistochemically examined. The nuclear expression of activated nuclear factor-kappaB, a major transcription factor of **iNOS** gene, was also immunohistochemically examined. RESULTS: In nontransgenic mice, SAH-induced **iNOS** protein and mRNA expressions in the arteries of basal cistern as well as in the cerebral cortex were demonstrated by immunohistochemistry and reverse transcription-polymerase chain reaction. SAH-induced **iNOS** protein and mRNA expressions in those tissues were much reduced in SOD-**transgenic mice** compared with nontransgenic mice. Moreover, the nuclear expression of the activated form of nuclear factor-kappaB was immunohistochemically detected in the cerebral cortices of nontransgenic mice but not in those of SOD-**transgenic mice**. CONCLUSIONS: These results indicate that oxygen-derived free radicals, particularly superoxide, play an

important role in the **iNOS** gene expression after SAH and provide a molecular basis for the protective role of SOD against vasospasm after SAH.

L14 ANSWER 29 OF 86 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 2001509406 MEDLINE
DOCUMENT NUMBER: 21440253 PubMed ID: 11556540
TITLE: **Inducible nitric oxide synthase** (**iNOS**) and nitrotyrosine immunoreactivity in the spinal cords of **transgenic mice** with a G93A mutant SOD1 gene.
AUTHOR: Sasaki S; Warita H; Abe K; Iwata M
CORPORATE SOURCE: Department of Neurology, Neurological Institute, Tokyo Women's Medical College, Japan.
SOURCE: JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (2001 Sep) 60 (9) 839-46.
Journal code: 2985192R. ISSN: 0022-3069.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20011001
Entered Medline: 20010927

AB We performed a prospective, longitudinal immunohistochemical study of the spinal cords of **transgenic mice** with a G93A mutant SOD1 gene at 4 fixed points in time, using antibodies to **inducible nitric oxide synthase** (**iNOS**) and nitrotyrosine. The purpose of this study was to characterize the temporal and topographic distribution of **iNOS** and nitrotyrosine immunoreactivity in the spinal cord over a certain period, thus illuminating the possible role of increased oxidative damage to the motor system in the neurodegenerative process in this animal model. Specimens from age-matched non-transgenic wild-type mice served as controls. The control mice showed no positive **iNOS** or nitrotyrosine immuunoreactivity in the somata of anterior horn neurons or their neuronal processes at any age. On the other hand, the **transgenic mice** demonstrated a common immunostaining pattern of **iNOS** and nitrotyrosine in the anterior horn neurons. When the mice reached the age of 24 wk (early presymptomatic stage), the anterior horn neurons and their neuronal processes were occasionally immunostained for **iNOS** and nitrotyrosine; at 28 wk (late presymptomatic stage), the anterior horn neurons were not uncommonly immunostained; at 32 wk (early symptomatic stage) and 35 wk (end-stage), positive **iNOS** and nitrotyrosine immunoreactivity was frequently observed in proliferated reactive astrocytes as well as in the somata of the anterior horn cells. The selective localization of positive **iNOS** and nitrotyrosine immunoreactivity in the anterior horn neurons suggests that oxidative stress may be involved in the pathomechanism of degeneration of motor neurons in this transgenic animal model.

L14 ANSWER 30 OF 86 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 2001543961 MEDLINE
DOCUMENT NUMBER: 21474427 PubMed ID: 11590196
TITLE: A defect in HIV-1 transgenic murine macrophages results in deficient nitric oxide production.
AUTHOR: Dickie P; Roberts A; Lee R
CORPORATE SOURCE: Department of Medical Microbiology and Immunology, University of Alberta, Edmonton, Alberta, Canada.. peter.dickie@ualberta.ca
SOURCE: JOURNAL OF LEUKOCYTE BIOLOGY, (2001 Oct) 70 (4) 592-600.
Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20011010
Last Updated on STN: 20011105
Entered Medline: 20011101

AB HIV **transgenic mice** bearing multiple copies of a noninfectious (Deltagag/pol) proviral DNA were tested for the systemic production of nitric oxide (NO). Serum levels of NO metabolites were reduced about 50% in HIV **transgenic mice** compared with nontransgenic sibling mice. This difference persisted when NO production was induced with peritoneal injections of bacterial endotoxin (LPS). Peritoneal inflammatory macrophages, but not resident peritoneal macrophages, derived from HIV-1 **transgenic mice** and activated in vitro with LPS and IFN-gamma (or tumor necrosis factor alpha and IFN-gamma) also produced about 50% less NO than did macrophages harvested from nontransgenic littermates. Isogenic, **transgenic mice** bearing mutated nef or vpr genes had normal serum levels of NO metabolites and their macrophages produced normal levels of NO when stimulated. An explanation for the reduced NO response of HIV[Vpr+Nef+] macrophages was not apparent from measured levels of **iNOS** expression, viral gene expression, or arginase activity in activated macrophages. Inhibition of nitric oxide synthase (NOS) isoforms with L-NAME or aminoguanidine blocked time-dependent increases in HIV gene expression in activated macrophages cultured ex vivo. Inhibition with L-NAME occurred despite high levels of NO generated by **iNOS**, and exogenously supplied NO induced HIV gene expression only weakly, suggesting that cNOS had the greater influence on proviral gene induction. This system is presented as a model of HIV-1 proviral gene expression and dysfunction in macrophages.

L14 ANSWER 31 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:6701 BIOSIS
DOCUMENT NUMBER: PREV200200006701
TITLE: **Inducible nitric oxide synthase** dependent blood pressure regulation in ET-1 **transgenic mice**.
AUTHOR(S): Hocher, B. (1); Schwarz, A. (1); Slowinski, T. (1); Bachmann, S.; Pfeilschifter, J.; Theuring, F.; Neumayer, H.-H. (1); Bauer, C.
CORPORATE SOURCE: (1) Department of Nephrology, Charite, Humboldt University of Berlin, Berlin Germany
SOURCE: Kidney & Blood Pressure Research, (2001) Vol. 24, No. 4-6, pp. 335. print.
Meeting Info.: Joint Scientific Meeting of the Nephrology Society and the German Working Group for Clinical Nephrology Munster, Germany September 29-October 02, 2001
ISSN: 1420-4096.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 32 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:478339 BIOSIS
DOCUMENT NUMBER: PREV200100478339
TITLE: Metallothionein I+II protect the CNS during neuroglial degeneration.
AUTHOR(S): Penkowa, M. (1); Giralt, M.; Camats, J.; Hidalgo, J.
CORPORATE SOURCE: (1) Dept Med Anatomy, Panum Inst, Univ. of Copenhagen, Copenhagen Denmark
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 298. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 6-Aminonicotinamide (6-AN) is a niacin antagonist, which leads to degeneration of grey matter astrocytes. Metallothionein I+II (MT-I+II) are neuroprotective factors in the CNS, and in order to determine the roles for MT after 6-AN, we have examined **transgenic mice** with overexpression of MT-I (TgMTI* mice) following an i.p. injection with 6-AN. In normal mice injected with 6-AN, astrocytes in specific grey matter areas of the brain stem showed degeneration. Reactive astrocytes surrounded the damaged areas, which were heavily infiltrated by macrophages and lymphocytes. MT-I+II expression was significantly decreased in the damaged brain stem areas, but it increased in astrocytes surrounding the damaged areas and also in infiltrating macrophages. The levels of oxidative stress, as determined by immunoreactivity for **inducible nitric-oxide synthase** (**iNOS**), malondialdehyde (MDA), and nitrotyrosine (NITT), and the number of TUNEL+, caspase-3+ apoptotic cells were increased in the brain stem of normal mice after 6-AN. In the TgMTI* mice, the 6-AN induced tissue damage was decreased in comparison to control mice, and TgMTI* mice showed significantly reduced numbers of recruited macrophages and lymphocytes, and a drastic reduction of oxidative stress and apoptotic cell death. In addition, the accompanying reactive astrogliosis was increased in TgMTI* mice. In order to further study the potential protective role of MT, we administered intraperitoneally Zn-MT-II to 6-AN injected normal mice and found essentially the same results as those obtained in TgMTI* mice. Thus, we hereby report that endogenous MT-I overexpression and exogenous MT-II treatment have significant neuroprotective roles during CNS pathological conditions.

L14 ANSWER 33 OF 86 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 2001:936336 SCISEARCH
THE GENUINE ARTICLE: 487UW
TITLE: Targeted disruption of **inducible nitric oxide synthase** does not improve the survival of **transgenic mice** with cytokine-induced cardiomyopathy
AUTHOR: Funakoshi H (Reprint); Kubota T; Kawamura N; Machida Y; Feldman A M; Takeshita A
CORPORATE SOURCE: Kyushu Univ, Grad Sch Med Sci, Fukuoka 812, Japan; Univ Pittsburgh, Med Ctr, Pittsburgh, PA USA
COUNTRY OF AUTHOR: Japan; USA
SOURCE: CIRCULATION, (23 OCT 2001) Vol. 104, No. 17, Supp. [S], pp. 196-196. MA 938.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L14 ANSWER 34 OF 86 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 2001634994 MEDLINE
DOCUMENT NUMBER: 21230509 PubMed ID: 11332990
TITLE: Regression of primary hepatocarcinoma in cancer-prone transgenic mice by local interferon-gamma delivery is associated with macrophages recruitment and nitric oxide production.
AUTHOR: Baratin M; Ziol M; Romieu R; Kayibanda M; Gouilleux F; Briand P; Leroy P; Haddada H; Renia L; Viguier M; Guillet J G
CORPORATE SOURCE: Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, ICGM, Laboratoire associe no 9 du comite de Paris de la Ligue Nationale contre le Cancer, France.. baratin@cochin.inserm.fr

SOURCE: CANCER GENE THERAPY, (2001 Mar) 8 (3) 193-202.
Journal code: 9432230. ISSN: 0929-1903.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20011105
Last Updated on STN: 20011105
Entered Medline: 20011101

AB The clinical potential of tumor therapies must be evaluated using animal models closely resembling human cancers. We investigated the impact of locally delivered interferon-gamma (IFN-gamma) on primary hepatocarcinoma spontaneously developed by T-SV40 **transgenic mice**. A single intratumor injection of adenovirus IFN-gamma was sufficient enough to induce in vivo production of biologically active IFN-gamma, as assessed by STAT1 activation. IFN-gamma secretion led to the regression of primary tumor, principally by apoptosis of tumor hepatocytes. The lack of T-cells infiltrates in the liver upon treatment excluded a role of a specific immune response. In contrast, indirect pathways may include tumoricidal function of macrophages. Indeed, they were massively recruited in the entire liver under IFN-gamma treatment; transmigration through hepatic blood vessels could be observed and co-localization with damaged hepatocytes was obvious. This correlated with nonparenchymal liver cell **iNOS** expression and high level of NO in hepatic extracts. Moreover, in vitro experiments showed that NO releasing agents induced cell death of freshly isolated tumor hepatocytes, suggesting that NO could be one of the major effector molecules. Altogether, these observations defined an important role of IFN-gamma in controlling tumor development in a model of primary hepatocarcinoma.

L14 ANSWER 35 OF 86 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 2002037110 MEDLINE
DOCUMENT NUMBER: 21608774 PubMed ID: 11764933
TITLE: Nitric oxide and peroxynitrite in ozone-induced lung injury.
AUTHOR: Laskin D L; Fakhrzadeh L; Laskin J D
CORPORATE SOURCE: Environmental and Occupational Health Sciences Institute and Department of Pharmacology and Toxicology, Rutgers University, Piscataway, NJ 08854, USA.
CONTRACT NUMBER: ES04738 (NIEHS)
ES06897 (NIEHS)
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (2001) 500 183-90. Ref: 39
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20020727
Entered Medline: 20020726

AB One of the hallmarks of the inflammatory response associated with tissue injury is the accumulation of macrophages at sites of damage. These cell types release proinflammatory cytokines and cytotoxic mediators to destroy invading pathogens and initiate wound repair. However, when produced in excessive amounts, these macrophage-derived mediators may actually contribute to tissue injury. This process involves both direct damage to target tissues and amplification of the inflammatory response. One group of macrophage-derived mediators of particular interest are reactive nitrogen intermediates including nitric oxide and peroxynitrite which have been implicated in tissue injury induced by a variety oftoxicants. Our

laboratory has been investigating the role of reactive nitrogen intermediates in lung injury induced by oxidants such as ozone. Inhalation of ozone causes epithelial cell damage and Type II cell hyperplasia. This is associated with an accumulation of activated macrophages in the lower lungs which we have demonstrated contribute to toxicity. To analyze the role of macrophage-derived reactive nitrogen intermediates in ozone toxicity, we used **transgenic mice** lacking the gene for **inducible nitric oxide synthase** (NOSII). Treatment of wild type control animals with ozone (0.8 ppm) for 3 hr resulted in an increase in bronchoalveolar lavage (BAL) fluid protein reaching a maximum 24-48 hr after exposure. This was correlated with increased expression of NOSII protein and mRNA by alveolar macrophages and increased production of nitric oxide as well as peroxynitrite. Ozone inhalation also resulted in the appearance of nitrotyrosine residues in the lungs, an in vivo marker of peroxynitrite-induced damage. In contrast, in NOSII knockout mice, BAL protein was not increased demonstrating that these mice were protected from ozone-induced epithelial injury. Moreover, alveolar macrophages from the **transgenic mice** did not produce nitric oxide or peroxynitrite even after ozone inhalation. There was also no evidence for the formation of nitrotyrosine in lung tissue. These data indicate that ozone-induced lung injury is mediated by reactive nitrogen intermediates.

L14 ANSWER 36 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:183214 BIOSIS
DOCUMENT NUMBER: PREV200100183214
TITLE: Uterine contractility in pregnant mice lacking an inducible nitric oxide synthase.
AUTHOR(S): Longo, Monica (1); Jain, Venu (1); Mackay, Lyn (1); Vedernikov, Yuri (1); Facchinetti, Fabio; Saade, George (1); Garfield, Robert (1)
CORPORATE SOURCE: (1) Ob/Gyn, University of Texas Medical Branch at Galveston, Galveston, TX USA
SOURCE: American Journal of Obstetrics and Gynecology, (January, 2001) Vol. 184, No. 1, pp. S78. print.
Meeting Info.: 21st Annual Meeting of the Society for Maternal-Fetal Medicine Reno, Nevada, USA February 05-10, 2001
ISSN: 0002-9378.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB OBJECTIVE: To study the role of nitric oxide (NO)-cGMP system in the maintenance of uterine quiescence using **transgenic mice** lacking an inducible NO synthase (**iNOS**). STUDY DESIGN: Uterine ring obtained from nonpregnant (n = 4-6) and timed-pregnant (n = 6-8, mid: day 14 and term: day 19) female **iNOS** knockout mice (KO, B6/129FJNOS2-/-, Jackson Laboratory) and their wild-type controls (WT, NOS2+/+) were mounted in organ chambers in Krebs solution for isometric tension recording. Uterine contractility was stimulated with oxytocin (10-9 M) and the effects of cumulative concentrations of NO donor sodium nitroprusside (SNP, 10-8-10-4 M), cGMP analogue 8-br-cGMP (10-8-10-4 M), NOS substrate L-arginine (10-6-10-3 M), ATP-dependent K+-channel opener, pinacidil (10-8-10-4 M), and Mg2+ (2-16 mM) were studied. RESULTS: Responses to the agents studied were not significantly different in non-pregnant WT and KO mice. At term, inhibition of uterine contractility by L-arginine, SNP and 8-br-cGMP was decreased compared to mid gestation in WT but not KO. Effects of L-arginine and SNP were significantly greater in WT compared to KO in mid-pregnancy and vice versa at term. Effect of 8-br-cGMP was significantly greater in KO compared to WT at term. Inhibition by pinacidil was lower, albeit not significantly, in pregnant compared to nonpregnant KO and WT. Responses to Mg2+ were not different between the groups. CONCLUSIONS: The NO-cGMP system is present in the uterus in nonpregnant and pregnant mice and is downregulated at term. Lack of **iNOS** during pregnancy is associated with changes in NO

production and sensitivity of the myometrium to NO and cGMP. The effects of ATP-dependent K+-channel and Mg2+ on uterine contractility are independent of **iNOS**.

L14 ANSWER 37 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 23
ACCESSION NUMBER: 2002:135313 BIOSIS
DOCUMENT NUMBER: PREV200200135313
TITLE: Effect of pregnancy on vascular reactivity in **transgenic mice** lacking a functional endothelial or **inducible nitric oxide synthase**.
AUTHOR(S): Longo, Monica (1); Jain, Venu (1); Vedernikov, Yuri; Saade, George (1); Garfield, Robert (1)
CORPORATE SOURCE: (1) Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TX USA
SOURCE: American Journal of Obstetrics and Gynecology, (December, 2001) Vol. 185, No. 6 Supplement, pp. S74. http://www.mosby.com/ajog. print.
Meeting Info.: 22nd Annual Meeting of the Society for Maternal-Fetal Medicine New Orleans, Louisiana, USA January 14-19, 2002
ISSN: 0002-9378.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 38 OF 86 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 2001394927 MEDLINE
DOCUMENT NUMBER: 21186302 PubMed ID: 11290390
TITLE: Fibrillary beta-amyloid deposits are closely associated with atrophic nitric oxide synthase (NOS)-expressing neurons but do not upregulate the inducible NOS in transgenic Tg2576 mouse brain with Alzheimer pathology.
AUTHOR: Hartlage-Rubsamen M; Apelt J; Schliebs R
CORPORATE SOURCE: Paul Flechsig Institute for Brain Research, Department of Neurochemistry, University of Leipzig, Jahnallee 59, D-04109, Leipzig, Germany.
SOURCE: NEUROSCIENCE LETTERS, (2001 Apr 20) 302 (2-3) 73-6.
Journal code: 7600130. ISSN: 0304-3940.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712

AB **Transgenic mice** (Tg2576) that express the Swedish double mutation of human amyloid precursor protein and develop Alzheimer-like beta-amyloid deposits in the aged brain, were used to study the effect of beta-amyloid deposition on expression of both neuronal (nNOS) and **inducible nitric oxide synthase** (**iNOS**) in cells surrounding beta-amyloid plaques. Nicotinamide adenine dinucleotide phosphate-diaphorase histochemistry and double immunofluorescent labeling revealed that most of the fibrillary, thioflavine-S-positive cortical beta-amyloid deposits in 13-, 17-, and 21-month-old transgenic animals were closely associated with dystrophic nNOS-positive neurons, while nNOS-bearing neurons located more distal to plaques appeared to be unaffected. There was no significant expression of **iNOS** in **transgenic mouse** brain. The data suggest enhanced vulnerability of nNOS-containing neocortical neurons to beta-amyloid toxicity. Alternatively, expression of nNOS may also be a response to plaque-mediated damage of neurons, consistent with a neuroprotective role of nitric oxide.

L14 ANSWER 39 OF 86 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 2001639663 MEDLINE
DOCUMENT NUMBER: 21547857 PubMed ID: 11689164
TITLE: Reduced activity and protein expression of NOS in R6/2 HD transgenic mice: effects of L-NAME on symptom progression.
AUTHOR: Deckel A W; Gordinier A; Nuttal D; Tang V; Kuwada C; Freitas R; Gary K A
CORPORATE SOURCE: Department of Psychiatry, University of Connecticut Medical School, 263 Farmington Avenue, Farmington, CT 06030-2103, USA.. deckel@psychiatry.uchc.edu
SOURCE: BRAIN RESEARCH, (2001 Nov 16) 919 (1) 70-81.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20020125
Entered Medline: 20020103

AB Previous work found that dietary l-arginine alters symptom progression in mice transgenic for Huntington's disease (HD), and that cerebral blood flow (CBF) is abnormal in early stage HD patients. Both of these findings potentially implicate nitric oxide (NO) and its converting enzyme, nitric oxide synthase (NOS), in HD. The current experiment found that both NOS enzymatic activity and neuronal NOS (nNOS) protein expression were reduced ($P<0.05$) in R6/2 HD **transgenic mice** compared to non-HD controls (CON). Conversely, inducible NOS (**iNOS**) protein expression was not significantly different between groups. The changes in nNOS were accompanied by changes in protein expression of calmodulin kinase II (CaMKII) ($P<0.05$) and calmodulin kinase IV (CaMKIV) ($P<0.05$). Protein expression of 3-nitrotyrosine (3-NT), a marker for the neurotoxin peroxynitrite, was slightly increased in non-drug treated HD and was accompanied by increased immunostaining of 3-NT in cells adhering to the vasculature and choroid plexus. Mice that received the broad-spectrum NOS inhibitor N(g)-nitro-L-arginine methyl ester hydrochloride (L-NAME) via their drinking water had reduced NOS enzyme activity. NOS activity varied as a function of L-NAME dose, was virtually eliminated in the 500-mg/l groups, and correlated ($P<0.05$) with the behavioral scores as revealed by regression and correlation analyses. High dose L-NAME (500 mg/l) accelerated symptom onset in HD transgenics. These results support the hypothesis that nNOS activity and NO production are abnormal in HD, this in the setting of a more global dysregulation of calcium protein expression. Taken collectively with earlier data from our laboratory demonstrating abnormal CBF findings in early-stage HD patients, these results suggest that abnormalities in NOS function may significantly contribute to the neurodegeneration found in HD.

L14 ANSWER 40 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 26
ACCESSION NUMBER: 2002:112515 BIOSIS
DOCUMENT NUMBER: PREV200200112515
TITLE: **Inducible nitric oxide synthase** expression and nitrotyrosine formation in humans and knockout-**transgenic mice** with sickle cell disease.
AUTHOR(S): Aslan, Mutay (1); Ryan, Thomas; Townes, Tim; Baldus, Stephan; Freeman, Bruce
CORPORATE SOURCE: (1) Department of Anesthesiology, Center for Free Radical Biology and Comprehensive Sickle Cell Disease Center, University of Alabama at Birmingham, Birmingham, AL, 35233 USA
SOURCE: Free Radical Biology & Medicine, (November, 2001) Vol. 31, No. 10, pp. S67. print.
Meeting Info.: 8th Annual Meeting of the Oxygen Society

Research Triangle Park, North Carolina, USA November 15-19, 2001
ISSN: 0891-5849.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 41 OF 86 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 2001489944 MEDLINE
DOCUMENT NUMBER: 21423196 PubMed ID: 11532247
TITLE: Expression of endothelial and inducible NOS-isoforms is increased in Alzheimer's disease, in APP23 transgenic mice and after experimental brain lesion in rat: evidence for an induction by amyloid pathology.
AUTHOR: Luth H J; Holzer M; Gartner U; Staufenbiel M; Arendt T
CORPORATE SOURCE: Department of Neuroanatomy, Paul Flechsig Institute of Brain Research, University of Leipzig, Jahnallee 59, D-04109 Leipzig, Germany.. lueth@medizin.uni-leipzig.de
SOURCE: BRAIN RESEARCH, (2001 Sep 14) 913 (1) 57-67.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010905
Last Updated on STN: 20020122
Entered Medline: 20011212

AB The nitric oxide-synthesizing enzyme nitric oxide synthase (NOS) is present in the mammalian brain in three different isoforms, two constitutive enzymes (i.e., neuronal, nNOS, and endothelial eNOS) and one inducible enzyme (**iNOS**). All three isoforms are aberrantly expressed in Alzheimer's disease giving rise to elevated levels of nitric oxide apparently involved in the pathogenesis of this disease by various different mechanisms including oxidative stress and activation of intracellular signalling mechanisms. It still is a matter of debate, however, whether the abnormal expression of NOS isoforms has some primary importance in the pathogenetic chain and might thus be a potential therapeutic target or only reflects a secondary effect that occurs at more advanced stages of the disease process. To tackle this question, we analysed the expression of both eNOS and **iNOS** in patients with sporadic AD, in **transgenic mice** expressing human amyloid precursor protein (APP) with the Swedish double mutation under control of the Thy1 promotor (APP23 mice), and after electrolytic cortical lesion in rat, an experimental paradigm associated with elevated expression of APP. In all three conditions, an astrocytosis was induced accompanied by a strong increase of both **iNOS** and eNOS. Both NOS isoforms were frequently though not always colocalized. Thus, based on the expression pattern of NOS isoforms three types of astrocytes, expressing only one of the two isoforms or both together could be distinguished. In both AD and **transgenic mice** eNOS-expressing astrocytes exceeded **iNOS**-expressing astrocytes in number. Astrocytes with elevated levels of **iNOS** or eNOS were constantly seen in direct association with Abeta-deposits in AD and **transgenic mice** and were found in the vicinity of the lesion site in the rat cortex. The results of the present study show that expression of both **iNOS** and eNOS is increased in activated astrocytes under experimental conditions associated with elevated expression of APP (electrolytic brain lesion) or Abeta-deposition (APP23 **transgenic mice**). Therefore, it is suggested that altered expression of these NOS isoforms being part of AD pathology is secondary to the amyloid pathology and might not be primarily involved in the pathogenetic chain though it might contribute to the maintenance, self-perpetuation and progression of the neurodegenerative process.

L14 ANSWER 42 OF 86 BIOSIS

ACCESSION NUMBER: 2001:369502 BIOSIS
DOCUMENT NUMBER: PREV200100369502
TITLE: TGFbeta1 regulates **iNOS**/macrophage-dependent apoptosis in mammary adenocarcinoma in MMTV/activated c-neu **transgenic mice**.
AUTHOR(S): Katevas, Prokopis (1); Bowe, Damon B. (1); Adereth, Yair (1); Maroulakou, Ioanna G. (1)
CORPORATE SOURCE: (1) Medical University of South Carolina, Charleston, SC USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 40-41. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L14 ANSWER 43 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:263970 BIOSIS
DOCUMENT NUMBER: PREV200200263970
TITLE: Targeted disruption of **inducible nitric oxide synthase** does not improve the survival of **transgenic mice** with cytokine-induced cardiomyopathy.
AUTHOR(S): Funakoshi, Hajime (1); Kubota, Toru (1); Kawamura, Natsumi (1); Machida, Yoji (1); Feldman, Arthur M.; Takeshita, Akira
CORPORATE SOURCE: (1) Graduate Sch of Med Sciences, Kyushu Univ, Fukuoka Japan
SOURCE: Circulation, (October 23, 2001) Vol. 104, No. 17 Supplement, pp. II.196. http://circ.ahajournals.org/. print.
Meeting Info.: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 44 OF 86 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 28
ACCESSION NUMBER: 2000:84538 CAPLUS
DOCUMENT NUMBER: 132:118350
TITLE: Transgenic mouse model of human oxidative stress comprising a human nitric oxide synthase gene (NOS2), and therapeutic uses thereof
INVENTOR(S): Vitek, Michael P.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000004770	A1	20000203	WO 1999-US16338	19990719
W: AU, CA, JP, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 9951134	A1	20000214	AU 1999-51134	19990719
PRIORITY APPLN. INFO.:			US 1998-93546P P	19980721
			WO 1999-US16338 W	19990719

AB The invention provides a **transgenic mouse** whose germ cells and somatic cells contain: i) an inactive mouse **inducible**

nitric oxide synthase gene (NOS2 gene); and
ii) a transgene encoding an active human NOS2 gene, with said transgene including all regulatory elements of the human nitric oxide synthase gene necessary for human patterns of expression of the transgene in the mouse. The transgenic mice of the invention are useful as models of human oxidative stress and can be used to study the role of nitric oxide in diseases such as Alzheimer's, multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis. The invention is particularly useful in evaluating the ability of compds. to induce or treat such diseases.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 45 OF 86 PCTFULL COPYRIGHT 2003 Univentio

ACCESSION NUMBER: 2000060117 PCTFULL ED 20020515
TITLE (ENGLISH): PREDICTION OF RISK OF INTERSTITIAL LUNG DISEASE
TITLE (FRENCH): PREDICTION DES RISQUES DE PATHOLOGIE INTERSTITIELLE PULMONAIRE
INVENTOR(S): DUFF, Gordon, W.; DI GIOVINE, Francesco, Saverio; WHYTE, Moria
PATENT ASSIGNEE(S): INTERLEUKIN GENETICS, INC.; DUFF, Gordon, W.; DI GIOVINE, Francesco, Saverio; WHYTE, Moria
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000060117	A2	20001012
DESIGNATED STATES	AE AU BR CA CN CZ HU IL JP KR MX NO NZ PL RU SG TR US YU ZA AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 2000-US8492	A	20000331
PRIORITY INFO.:	US 1999-09/286,108		19990402

ABEN The present invention provides novel methods and kits for determining whether a subject has or is likely to develop an interstitial lung disorder such as pulmonary fibrosis; as well as methods for treating an ILD and screening assays for identifying novel ILD therapeutics.

ABFR L'invention concerne des methodes et des kits nouveaux permettant de determiner si un sujet est atteint d'une pathologie interstitielle pulmonaire ou s'il est susceptible de developper une telle pathologie, telle que la fibrose pulmonaire. L'invention concerne egalement des methodes de traitement d'une pathologie interstitielle pulmonaire et des essais de criblage pour identifier de nouvelles therapeutiques contre ces pathologies.

L14 ANSWER 46 OF 86 PCTFULL COPYRIGHT 2003 Univentio

ACCESSION NUMBER: 2000044766 PCTFULL ED 20020515
TITLE (ENGLISH): INHIBITION OF CATIONIC AMINO ACID TRANSPORTER PROTEIN AND USES THEREOF
TITLE (FRENCH): INHIBITION D'UNE PROTEINE TRANSPORTEUSE D'ACIDES AMINES CATIONIQUES ET SES UTILISATIONS
INVENTOR(S): MACLEOD, Carol, L.
PATENT ASSIGNEE(S): RESEARCH DEVELOPMENT FOUNDATION
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000044766	A1	20000803
DESIGNATED STATES	AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX		

NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM
AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB
GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML
MR NE SN TD TG

APPLICATION INFO.: WO 2000-US2041 A 20000127
PRIORITY INFO.: US 1999-09/238,972 19990127

ABEN The present invention provides methods of inhibiting cationic amino acid transport by means of antisense and antibody technology specific for the CAT2 transporter. Further, the present invention provides methods of treating a disease characterized by undesirable levels of nitric oxide.

ABFR La presente invention concerne des procedes qui permettent d'inhiber le transport d'acides amines cationiques au moyen d'une technique antisens et anticorps specifique au transporteur CAT2. L'invention concerne en outre des procedes pour traiter une maladie caracterisee par des niveaux indesirables d'oxyde nitrique.

L14 ANSWER 47 OF 86 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 2000187488 MEDLINE
DOCUMENT NUMBER: 20187488 PubMed ID: 10722612
TITLE: Innate lung defenses and compromised Pseudomonas aeruginosa clearance in the malnourished mouse model of respiratory infections in cystic fibrosis.
AUTHOR: Yu H; Nasr S Z; Deretic V
CORPORATE SOURCE: Departments of Microbiology, University of Michigan Medical School, Ann Arbor, Michigan, USA.
CONTRACT NUMBER: AI31139 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (2000 Apr) 68 (4) 2142-7. Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000420

AB Cystic fibrosis (CF) is characterized by dysfunction of the digestive and respiratory tracts resulting in generalized malnutrition and chronic respiratory infections. Chronic lung infections with Pseudomonas aeruginosa, intense neutrophil-dominated airway inflammation, and progressive lung disease are the major cause of high morbidity and mortality in CF. Here we investigated the effects of malnutrition in CF on innate lung defenses, susceptibility to P. aeruginosa colonization, and associated inflammation, using aerosol models of acute and chronic infections in normal, malnourished, and **transgenic mice**. CFTR(m1Unc-/-) knockout mice displayed body weight variations and showed variable pulmonary clearance of P. aeruginosa. This variability was not detected in bitransgenic CFTR(m1Unc-/-)(FABP-hCFTR) mice in which the intestinal defect had been corrected. Diet-induced protein calorie malnutrition in C57BL/6J mice resulted in impaired pulmonary clearance of P. aeruginosa. Tumor necrosis factor alpha (TNF-alpha) and nitrite levels detected upon exposure to P. aeruginosa aerosols were lower in the lungs of the malnourished C57BL/6J mice relative than in lungs of mice fed a normal diet. The role of TNF-alpha and reactive nitrogen intermediates in P. aeruginosa clearance was tested in TNF-alpha and **inducible nitric oxide synthase** (**iNOS**) knockout mice. P. aeruginosa clearance was diminished in transgenic TNF-alpha- and **iNOS**-deficient mice. In contrast to the effects of TNF-alpha and **iNOS**, gamma interferon knockout mice retained a full capacity to eliminate P. aeruginosa from the lung. Malnutrition also

contributed to excessive inflammation in C57BL/6J mice upon chronic challenge with P. aeruginosa. The repeatedly infected malnourished host did not produce interleukin-10, a major anti-inflammatory cytokine absent or diminished in the bronchoalveolar fluids of CF patients. These results are consistent with a model in which defective CFTR in the intestinal tract leads to nutritional deficiency which in turn contributes to compromised innate lung defenses, bacterial colonization, and excessive inflammation in the CF respiratory tract.

L14 ANSWER 48 OF 86 MEDLINE DUPLICATE 30
ACCESSION NUMBER: 2000238179 MEDLINE
DOCUMENT NUMBER: 20238179 PubMed ID: 10775120
TITLE: Protection against endotoxemia by HSP70 in rodent cardiomyocytes.
AUTHOR: Lau S S; Griffin T M; Mestril R
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Diego, La Jolla, California 92093-0618, USA.
CONTRACT NUMBER: K14-HL03150-01 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. HEART AND CIRCULATORY PHYSIOLOGY, (2000 May) 278 (5) H1439-45.
Journal code: 100901228. ISSN: 0363-6135.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000628

AB Clinical and experimental studies have shown that myocardial dysfunction is an early event during endotoxemia or septic shock. Several reports have shown that rodents submitted to a mild heat shock become resistant to lipopolysaccharides (LPS) or sepsis. The most abundant of the heat shock proteins (HSP), the HSP70, has been postulated to be the principal mediator of the observed protection against endotoxemia. We have tested the hypothesis that a protective effect against endotoxemia is achievable by the increased presence of the HSP70 in rodent cardiomyocytes. We have found that a **transgenic mouse** line overexpressing the rat HSP70 gene in the heart exhibits an increased tolerance to LPS treatment control estimated survival function [S(t)] = 0.538, transgenic S(t) = 0.787, P < 0.05 . Interestingly, the increased presence of the HSP70 in the hearts of these mice results in a decrease in the activation of the **inducible nitric oxide synthase** (**iNOS**) after LPS treatment. We conclude that HSP70 protection against LPS is most probably mediated through the modulation of **iNOS** activation and the subsequent decreased synthesis of nitric oxide in cardiomyocytes.

L14 ANSWER 49 OF 86 MEDLINE DUPLICATE 31
ACCESSION NUMBER: 2001055115 MEDLINE
DOCUMENT NUMBER: 20514022 PubMed ID: 11058547
TITLE: Relaxation of myometrium by calcitonin gene-related peptide is independent of nitric oxide synthase activity in mouse uterus.
AUTHOR: Naghashpour M; Dahl G
CORPORATE SOURCE: Department of Physiology and Biophysics, University of Miami School of Medicine, Miami, Florida 33101, USA.
CONTRACT NUMBER: GM48610 (NIGMS)
SOURCE: BIOLOGY OF REPRODUCTION, (2000 Nov) 63 (5) 1421-7.
Journal code: 0207224. ISSN: 0006-3363.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001215

AB Calcitonin gene-related peptide (CGRP) inhibits myometrial contractile activity. However, the responsiveness of the mouse myometrium to CGRP is dependent on the hormonal and gestational stage. The inhibitory effect of CGRP in the myometrium is prominent during gestation and declines at parturition. The present study was undertaken to examine if nitric oxide (NO) production by nitric oxide synthase (NOS) isoforms mediates the inhibitory action of CGRP on uterine contractions as has been suggested earlier. **Transgenic mice** deficient in either of the three major NOS isoforms: endothelial NOS (eNOS), inducible NOS (**iNOS**), and neuronal NOS (nNOS) were used. Isometric force measurements on myometrial strips obtained from NOS-deficient mice were carried out and the inhibitory capacity of CGRP was monitored. CGRP inhibited KCl-induced contractions of the myometrial strips obtained from eNOS(-/-), **iNOS**(-/-), and nNOS(-/-) mice with equal efficiency as in wild-type animals. Additionally, NOS protein expression in the mouse uterus during gestation and during the estrous cycle was examined by means of Western immunoblot analysis. No correlation between NOS expression and inhibitory activity of CGRP was evident. The results suggest that the inhibitory action of CGRP in the mouse uterus is independent of the activity of these NOS isoforms.

L14 ANSWER 50 OF 86 MEDLINE DUPLICATE 32
ACCESSION NUMBER: 2000213466 MEDLINE
DOCUMENT NUMBER: 20213466 PubMed ID: 10748242
TITLE: Nitric oxide inhibits hepatitis B virus replication in the livers of transgenic mice.
AUTHOR: Guidotti L G; McClary H; Loudis J M; Chisari F V
CORPORATE SOURCE: Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California 92037, USA.. guidotti@scripps.edu
CONTRACT NUMBER: AI09484 (NIAID)
AI40696 (NIAID)
CA40489 (NCI)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (2000 Apr 3) 191 (7) 1247-52.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000608

AB We have previously identified two antiviral cytokines (interferon [IFN]-gamma and IFN-alpha/beta) that downregulate hepatitis B virus (HBV) replication in the liver of **transgenic mice**. The cytokine-inducible downstream events that inhibit HBV replication have not been identified. One possible factor is nitric oxide (NO), a pleiotropic free radical with antiviral activity that is produced in the liver by the inducible NO synthase (**iNOS**). To examine the role of NO in our model, we crossed **transgenic mice** that replicate HBV with mice that lack a functional **iNOS**. Importantly, **iNOS**-deficient mice were almost completely resistant to the noncytopathic inhibitory effect of HBV-specific cytotoxic T lymphocytes on viral replication, an effect that we have shown previously to depend on the intrahepatic induction of IFN-gamma. Conversely, **iNOS**-deficient mice were not resistant to the antiviral effect of IFN-alpha/beta induced by either polyinosinic-polycytidylic acid complex or by lymphocytic choriomeningitis virus (LCMV) infection. These results indicate that NO mediates the antiviral activity of IFN-gamma, whereas the antiviral

activity of IFN-alpha/beta is NO independent. We also compared the relative sensitivity of LCMV to control by NO in these animals. Interestingly, LCMV replicated to higher levels in the liver of **iNOS**-deficient mice than control mice, indicating that NO controls LCMV replication in the liver, as well as HBV.

L14 ANSWER 51 OF 86 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:477454 CAPLUS
DOCUMENT NUMBER: 133:218708
TITLE: Inducible nitric oxide synthase mRNA is upregulated in skin tumors of v-Ha-ras transgenic TG-AC mice treated with 12-O-tetradecanoylphorbol-13-acetate
AUTHOR(S): Lee, Byung Mu; Kim, Hyung Sik; Jeohn, Gwang-Ho
CORPORATE SOURCE: Division of Toxicology, College of Pharmacy, SungKyunKwan University, Suwon, 440-746, S. Korea
SOURCE: Biological & Pharmaceutical Bulletin (2000), 23(7), 826-829
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The correlation between the steady-state level of inducible nitric oxide synthase (iNOS) mRNA and skin tumors induced following treatment with 12-o-tetradecanoylphorbol-13-acetate (TPA) was investigated in transgenic TG-AC mice, which carry the v-Ha-ras oncogene fused to the promoter of the mouse embryonic .alpha.-like, .zeta.-globin gene. In animals treated with TPA (2.5 .mu.g .times. 2/wk, for 2 wk), the increase of iNOS mRNA was locally confined only to the regions of papillomas, but not to the skin tissues surrounding the papillomas. However, the tissues surrounding the papillomas showed only a minor increase in the steady-state level of iNOS mRNA. These data suggest that iNOS gene expressions may underlie tumorigenesis during TPA promotion in TG-AC mice.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 52 OF 86 MEDLINE DUPLICATE 33
ACCESSION NUMBER: 2000227714 MEDLINE
DOCUMENT NUMBER: 20227714 PubMed ID: 10764411
TITLE: Increased microvascular reactivity and improved mortality in septic mice lacking inducible nitric oxide synthase.
AUTHOR: Hollenberg S M; Broussard M; Osman J; Parrillo J E
CORPORATE SOURCE: Sections of Critical Care and Cardiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612, USA.. shollenb@rpslmc.edu
CONTRACT NUMBER: R01GM57088 (NIGMS)
SOURCE: CIRCULATION RESEARCH, (2000 Apr 14) 86 (7) 774-8.
Journal code: 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20021210
Entered Medline: 20000512
AB Persistent vasodilation characteristic of septic shock may result from overproduction of nitric oxide and can lead to pressor-refractory hypotension and death. To evaluate the significance of cytokine-**inducible nitric oxide synthase** (**iNOS**) in the pathogenesis of sepsis, we used a clinically relevant mouse model of sepsis and compared mortality and microvascular reactivity in wild-type (WT) mice and **transgenic mice** deficient in **iNOS**. WT C57BL/6 and **iNOS**-deficient mice were made septic by cecal ligation and puncture. Treated mice were given fluids and antibiotics every 6 hours. Microvascular vasoconstriction in response to

topical norepinephrine was measured in cremasteric arterioles (15 to 30 microm) by videomicroscopy. Mortality at 48 hours was significantly lower in treated septic **iNOS**-deficient mice (45%) than in treated septic WT mice (76%), untreated septic **iNOS**-deficient mice (87%), or untreated WT mice (100%) (P<0.01). Norepinephrine-induced vasoconstriction was decreased in WT septic mice (EC(50) 200+/-56 nmol/L) compared with WT and **iNOS**-deficient shams (16+/-4 and 13+/-6 nmol/L), and vasoconstriction was significantly improved in septic **iNOS**-deficient mice (35+/-13 nmol/L, P<0.01). Microvascular catecholamine responsiveness and survival were improved in **iNOS** -deficient mice in a clinically relevant model of sepsis, suggesting that **iNOS** plays an important, but not exclusive, role in refractory vasodilation in patients with septic shock.

L14 ANSWER 53 OF 86 MEDLINE DUPLICATE 34
ACCESSION NUMBER: 2000410888 MEDLINE
DOCUMENT NUMBER: 20394244 PubMed ID: 10934296
TITLE: Expression of the inducible form of the nitric oxide synthase gene in the livers of mice with chronic hepatitis.
AUTHOR: Okamoto T; Yamamura K; Hino O
CORPORATE SOURCE: Research Laboratories, Nippon Chemiphar Co., Ltd., Saitama 341-0005, Japan.
SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, (2000 Sep) 6 (3) 315-7.
Journal code: 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000825

AB The interferon-gamma (IFN-gamma) **transgenic mouse** expresses the exogenous IFN-gamma gene in the liver and develops chronic hepatitis. For the present experiment, four IFN-gamma transgene (+) mice of 48 weeks of age and 16 IFN-gamma transgene (+) mice of 8 weeks of age were used. The four IFN-gamma transgene (+) mice of 48 weeks of age showed significantly elevated plasma alanine aminotransferase (ALT) and expressed the inducible form of nitric oxide synthase (**iNOS**) mRNA in the liver. Of the 16 IFN-gamma transgene (+) mice of 8 weeks of age, **iNOS** mRNA was expressed in the livers of three. These three mice exhibited higher plasma ALT levels than the other mice of 8 weeks of age. The present results suggest that **iNOS** mRNA expression in the liver might be correlated with the progression of hepatitis.

L14 ANSWER 54 OF 86 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:417247 CAPLUS
DOCUMENT NUMBER: 133:41258
TITLE: Roles of NO in cardiovascular system. Knowledge from studies on NOS gene-engineered mice
AUTHOR(S): Kawashima, Seinosuke
CORPORATE SOURCE: Sch. Med., Kobe Univ., Japan
SOURCE: Kekkan to Naihi (2000), 10(3), 283-290
CODEN: KENAE5; ISSN: 0917-5318
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 28 refs. The phenotypes of neuronal nitric oxide synthase (nNOS)-knockout mice, inducible NOS (**iNOS**)-knockout mice, endothelial NOS (eNOS)-knockout mice, and eNOS-overexpressing **transgenic mice** are described. Role of NO formed by nNOS in cerebral ischemia, involvement of iNOS-derived NO in apoptosis and oxidative stress, effects of eNOS-derived NO on cardiomyocytes and blood vessels, involvement of NO in vascular remodeling, and roles of NO in

cardiovascular diseases including arteriosclerosis are discussed.

L14 ANSWER 55 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:330163 BIOSIS
DOCUMENT NUMBER: PREV200000330163
TITLE: Regulation of nitric oxide release in human apolipoprotein-E targeted replacement mice and human **iNOS transgenic mice**.
AUTHOR(S): Brown, C. M. (1); Dawson, H. N. (1); Eyster, M. V. (1); Wright, E. (1); Sullivan, P. M. (1); Colton, C. A.; Vitek, M. P. (1)
CORPORATE SOURCE: (1) Duke University Medical Center, Durham, NC USA
SOURCE: Nitric Oxide, (2000) Vol. 4, No. 3, pp. 265. print.
Meeting Info.: First International Conference on Biology, Chemistry, and Therapeutic Applications of Nitric Oxide San Francisco, California, USA June 03-07, 2000
ISSN: 1089-8603.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L14 ANSWER 56 OF 86 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 2001:53933 SCISEARCH
THE GENUINE ARTICLE: 367QE
TITLE: Overexpression of **inducible nitric oxide synthase** in arterial smooth muscle cells of **transgenic mice**.
AUTHOR: Mungrue I N (Reprint); Gros R; You X M; Stewart D J; Husain M
CORPORATE SOURCE: Univ Toronto, Toronto, ON, Canada; Univ Hlth Network, Toronto, ON, Canada; Toronto Gen Hosp, Toronto, ON, Canada
COUNTRY OF AUTHOR: Canada
SOURCE: CIRCULATION, (31 OCT 2000) Vol. 102, No. 18, Supp. [S], pp. 151-151. MA 733.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L14 ANSWER 57 OF 86 MEDLINE DUPLICATE 35
ACCESSION NUMBER: 2000095965 MEDLINE
DOCUMENT NUMBER: 20095965 PubMed ID: 10632104
TITLE: Mitochondrial dysfunction and free radical damage in the Huntington R6/2 transgenic mouse.
AUTHOR: Tabrizi S J; Workman J; Hart P E; Mangiarini L; Mahal A; Bates G; Cooper J M; Schapira A H
CORPORATE SOURCE: University Department of Clinical Neurosciences, Royal Free and University College Medical School, London, UK.
SOURCE: ANNALS OF NEUROLOGY, (2000 Jan) 47 (1) 80-6.
Journal code: 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000216
AB Huntington's disease is a progressive neurodegenerative disease caused by an abnormally expanded (>36) CAG repeat within the ITI5 gene encoding a widely expressed 349-kd protein, huntingtin. The medium spiny neurons of the caudate preferentially degenerate in Huntington's disease, with the presence of neuronal intranuclear inclusions. Excitotoxicity is thought to

be important in the pathogenesis of Huntington's disease; the recently described mitochondrial respiratory chain and aconitase defects in Huntington's disease brain are consistent with this hypothesis. A **transgenic mouse** model (R6/2) of Huntington's disease develops a movement disorder, muscle wasting, and premature death at about 14 to 16 weeks. Selective neuronal death in these mice is not seen until 14 weeks. Biochemical analysis of R6/2 mouse brain at 12 weeks demonstrated a significant reduction in aconitase and mitochondrial complex IV activities in the striatum and a decrease in complex IV activity in the cerebral cortex. Increased immunostaining for **inducible nitric oxide synthase** and nitrotyrosine was seen in the **transgenic mouse** model but not control mouse brains. These results extend the parallels between Huntington's disease and the **transgenic mouse** model to biochemical events and suggest complex IV deficiency and elevated nitric oxide and superoxide radical generation precede neuronal death in the R6/2 mouse and contribute to pathogenesis.

L14 ANSWER 58 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:113530 BIOSIS
DOCUMENT NUMBER: PREV200100113530
TITLE: Overexpression of **inducible nitric oxide synthase** in arterial smooth muscle cells of **transgenic mice**.
AUTHOR(S): Mungrue, Imran N. (1); Gros, Robert; You, Xiao-Mang; Stewart, Duncan J.; Husain, Mansoor
CORPORATE SOURCE: (1) Univ of Toronto, Toronto, ON Canada
SOURCE: Circulation, (October 31, 2000) Vol. 102, No. 18 Supplement, pp. II.151. print.
Meeting Info.: Abstracts from Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L14 ANSWER 59 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:97823 BIOSIS
DOCUMENT NUMBER: PREV200100097823
TITLE: Role of NOS isoforms in the course of bacterial meningitis.
AUTHOR(S): Winkler, F. (1); Koedel, U.; Paul, R.; Huang, P. L.; Pfister, H. W.
CORPORATE SOURCE: (1) LMU, Munich Germany
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-398.10. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Nitric oxide (NO) production in the CNS is increased during bacterial meningitis. However, the source of NO and its role in the pathogenesis of this disease is still unclear. The aim of our study was (1) to determine the differential expression of endothelial NO synthase (eNOS), neuronal NOS (nNOS), and inducible NOS (**iNOS**) in the course of experimental meningitis, and (2) to clarify the pathophysiologic relevance of eNOS using **transgenic mice**. Mice were infected intracisternally with pneumococci. RT-PCR and immunohistochemistry were performed with frozen sections from total brain 0, 4, 8, and 24 hours after infection (p.i.). In wild type mice, a significant increase in cerebral eNOS mRNA expression was detected 8 and 24 hours p.i. A moderate induction of **iNOS** mRNA expression occured 4 hours p.i. and further increased to marked levels by 24 hours. There was no significant

time-dependent change in nNOS expression. Immunohistochemistry revealed a marked increase in endothelial eNOS staining 24 hours p.i. **iNOS** -immunoreactivity was present only in infiltrating leucocytes. In infected eNOS-deficient mice, there was a significantly increased mortality rate compared to wild type mice (53% vs. 19%), and meningitis-associated pathophysiological alterations were aggravated. Our findings suggest that eNOS and **iNOS** are the sources of elevated NO production during bacterial meningitis and that eNOS seems to play a protective role in this disease. The early induction and marked upregulation of **iNOS** in mouse brain point to the importance of further studies to elucidate the specific role of this isoform in the pathophysiology of bacterial meningitis.

L14 ANSWER 60 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:75646 BIOSIS
DOCUMENT NUMBER: PREV200100075646
TITLE: Effects of inducible nitric oxide synthase inhibitors in a transgenic model of amyotrophic lateral sclerosis.
AUTHOR(S): Friedlich, A. L. (1); Brandman, S. J.; Aguirre, N.; Shinobu, L. A.; Beal, M. F.
CORPORATE SOURCE: (1) Weill Medical College of Cornell Universtiy, New York, NY USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-85.10. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Nitric oxide has been proposed as an important player in the pathogenesis of amyotrophic lateral sclerosis (ALS) through its reaction with the superoxide anion to form peroxynitrite. Expression of the inducible isoform of nitric oxide synthase (**iNOS**) is increased in the spinal cords of **transgenic mice** carrying the G93A mutation in CuZn superoxide dismutase (CuZn SOD; Almer et al., 1999, J. Neurochem., 72:2415) and may be increased in ALS spinal cords (Phul et al., 1998, J. Neurol. Sci., 160:S87). To investigate the role of **iNOS** activity in the pathogenesis of ALS, we administered the **iNOS** inhibitors aminoguanidine and N-iminoethyl-L-lysine (L-NIL) to G93A **transgenic mice**. Administration of aminoguanidine in the drinking water (1 g/L) beginning at 50 days of age (n=12) increased the age of onset of hind limb paralysis and increased survival, with trends toward statistical significance. Furthermore, aminoguanidine treatment significantly improved motor performance on a rotarod apparatus at 110 and 120 days of age. Administration of L-NIL (1.68 g/L) in the drinking water beginning at 48 days of age (n=9) increased the age of onset of hind limb paralysis and increased survival, with trends toward statistical significance. These results will be discussed, and additional work will be presented.

L14 ANSWER 61 OF 86 MEDLINE DUPLICATE 36
ACCESSION NUMBER: 1999277354 MEDLINE
DOCUMENT NUMBER: 99277354 PubMed ID: 10349851
TITLE: **Inducible nitric oxide synthase** up-regulation in a **transgenic mouse** model of familial amyotrophic lateral sclerosis.
AUTHOR: Almer G; Vukosavic S; Romero N; Przedborski S
CORPORATE SOURCE: Department of Neurology, Columbia University, New York, New York 10032, USA.
CONTRACT NUMBER: R29 NS37345 (NINDS)
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1999 Jun) 72 (6) 2415-25.
Journal code: 2985190R. ISSN: 0022-3042.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990614

AB Mutations in copper/zinc superoxide dismutase (SOD1) are associated with a familial form of amyotrophic lateral sclerosis (ALS), and their expression in **transgenic mice** produces an ALS-like syndrome. Here we show that, during the course of the disease, the spinal cord of **transgenic mice** expressing mutant SOD1 (mSOD1) is the site not only of a progressive loss of motor neurons, but also of a dramatic gliosis characterized by reactive astrocytes and activated microglial cells. These changes are absent from the spinal cord of age-matched **transgenic mice** expressing normal SOD1 and of wild-type mice. We also demonstrate that, during the course of the disease, the expression of **inducible nitric oxide synthase** (**iNOS**) increases. In both early symptomatic and end-stage transgenic mSOD1 mice, numerous cells with the appearance of glial cells are strongly **iNOS**-immunoreactive. In addition, **iNOS** mRNA level and catalytic activity are increased significantly in the spinal cord of these transgenic mSOD1 mice. None of these alterations are seen in the cerebellum of these animals, a region unaffected by mSOD1. Similarly, no up-regulation of **iNOS** is detected in the spinal cord of age-matched **transgenic mice** expressing normal SOD1 or of wild-type mice. The time course of the spinal cord gliosis and **iNOS** up-regulation parallels that of motor neuronal loss in transgenic mSOD1 mice. Neuronal nitric oxide synthase expression is only seen in neurons in the spinal cord of transgenic mSOD1 mice, regardless of the stage of the disease, and of age-matched **transgenic mice** expressing normal SOD1 and wild-type mice. Collectively, these data suggest that the observed alterations do not initiate the death of motor neurons, but may contribute to the propagation of the neurodegenerative process. Furthermore, the up-regulation of **iNOS**, which in turn may stimulate the production of nitric oxide, provides further support to the presumed deleterious role of nitric oxide in the pathogenesis of ALS. This observation also suggests that **iNOS** may represent a valuable target for the development of new therapeutic avenues for ALS.

L14 ANSWER 62 OF 86 MEDLINE DUPLICATE 37
ACCESSION NUMBER: 1999440859 MEDLINE
DOCUMENT NUMBER: 99440859 PubMed ID: 10512307
TITLE: Effects of ethanol on neutrophil recruitment and lung host defense in nitric oxide synthase I and nitric oxide synthase II knockout mice.
AUTHOR: Greenberg S S; Ouyang J; Zhao X; Parrish C; Nelson S; Giles T D
CORPORATE SOURCE: Department of Medicine, Louisiana State University Medical Center, New Orleans 70112, USA.
CONTRACT NUMBER: 1P05-AA09803 (NIAAA)
RO1-AA-09816 (NIAAA)
SOURCE: ALCOHOLISM, CLINICAL AND EXPERIMENTAL RESEARCH, (1999 Sep) 23 (9) 1435-45.
Journal code: 7707242. ISSN: 0145-6008.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991102

AB BACKGROUND: Ethanol (ETOH) inhibits Escherichia coli endotoxin [lipopolysaccharide (LPS)]-mediated induction of nitric oxide (NO) synthase (NOS) transcription and translation in macrophages and neutrophils [polymorphonuclear (PMN) cells] within the lung. ETOH also inhibits PMN recruitment into the lung and enhances NOS I-mediated production of NO. The contribution of the individual NOS isozymes to ETOH-mediated suppression of the host defense response to lung infection has not been defined. METHODS: We evaluated the role of constitutive NOS I and NOS II in ETOH-mediated inhibition of PMN recruitment into the lung and ETOH-mediated suppression of lung clearance of inhaled Klebsiella pneumonia (K. pneumoniae) in female, homozygous **transgenic mice** deficient in the genes for NOS I (nNOS-KO) or NOS II (**iNOS**-KO) and their wild-type controls (WT). RESULTS: Four hours after intratracheal administration of LPS or aerosol inhalation of K. pneumoniae, the lung content of PMNs obtained by bronchoalveolar lavage from WT mice was significantly reduced when compared with that obtained from the lungs of nNOS-KO and **iNOS**-KO mice. Pretreatment of WT mice with the NOS II inhibitor L-N6-iminoethyllysine (L-NIL; 10 mg/kg, i.p.) or with the NOS I inhibitor 7-nitroindazole (7-NI) (10, 25, or 40 mg/kg, i.p.) 30 min before LPS administration enhanced the lung content of PMNs recoverable by bronchoalveolar lavage. However, pretreatment of **iNOS**-KO with L-NIL did not affect lung recruitment of PMNs. Moreover, administration of 25 or 40 mg/kg, i.p. of 7-NI to nNOS-KO mice resulted in death of all the animals within 10 min. Pretreatment of nNOS-KO with 7-NI (10 mg/kg) did not affect LPS-stimulated PMN recruitment. Pretreatment of mice with ETOH (4.5 g/kg, i.p.) produced a greater inhibition of LPS-stimulated lung recruitment of PMNs in **iNOS**-KO mice than in WT mice. In contrast, pretreatment of nNOS-KO with ETOH produced little inhibition of LPS-stimulated lung recruitment of PMNs when compared with that measured in WT mice. Finally, 4 hr after aerosol inhalation of K. pneumoniae, lung clearance of this bacteria was enhanced in **iNOS**-KO when compared with WT and inhibited in nNOS-KO when compared with WT mice. ETOH-mediated suppression of lung clearance of K. pneumoniae was unaffected in nNOS-KO mice and enhanced in the **iNOS**-KO mice, when compared with that obtained in WT mice. ETOH-stimulated the production of NOS I-derived nitrate and nitrite production by rat brain and lung and inhibited LPS-induced NOS II mRNA, protein, and production of nitrate and nitrite anion. Finally, inhibition of NOS I and NOS I deletion inhibited the in vivo metabolism of ETOH. CONCLUSIONS: We conclude that constitutive NOS I is involved in protection of the lung from stressor-induced lung injury. NOS I within the PMNs may limit PMN recruitment into the lung. Speculatively, NOS II-derived NO may also limit PMN-induced lung damage at the expense of a slower clearance of the bacterial burden.

L14 ANSWER 63 OF 86 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1999:972303 SCISEARCH
THE GENUINE ARTICLE: 250YD
TITLE: Myocardial overexpression of human **inducible nitric oxide synthase** [**iNOS**] in **transgenic mice** is cardiotoxic
AUTHOR: Mungrue I N (Reprint); Stewart D J; You X M; Azad A; Husain M
CORPORATE SOURCE: UNIV TORONTO, TORONTO, ON, CANADA; ST MICHAELS HOSP, TORONTO, ON M5B 1W8, CANADA; TORONTO GEN HOSP, TORONTO, ON, CANADA; CTR CV RES, TORONTO, ON, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: CIRCULATION, (2 NOV 1999) Vol. 100, No. 18, Supp. [S], pp. 580-580.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN

LANGUAGE: English
REFERENCE COUNT: 0

L14 ANSWER 64 OF 86 MEDLINE DUPLICATE 38
ACCESSION NUMBER: 1999413962 MEDLINE
DOCUMENT NUMBER: 99413962 PubMed ID: 10484454
TITLE: Relative contributions of endothelial, inducible, and neuronal NOS to tone in the murine pulmonary circulation.
AUTHOR: Fagan K A; Tyler R C; Sato K; Fouty B W; Morris K G Jr; Huang P L; McMurtry I F; Rodman D M
CORPORATE SOURCE: Cardiovascular Pulmonary Research Laboratory, University of Colorado Health Sciences Center, Denver, Colorado 80262, USA.. karen.fagan@uchsc.edu
CONTRACT NUMBER: HL-14985 (NHLBI)
HL-48038 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 Sep) 277 (3 Pt 1) L472-8.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991028

AB Nitric oxide plays an important role in modulating pulmonary vascular tone. All three isoforms of nitric oxide synthase (NOS), neuronal (nNOS, NOS I), inducible (**iNOS**, NOS II), and endothelial (eNOS, NOS III), are expressed in the lung. Recent reports have suggested an important role for eNOS in the modulation of pulmonary vascular tone chronically; however, the relative contribution of the three isoforms to acute modulation of pulmonary vascular tone is uncertain. We therefore tested the effect of targeted disruption of each isoform on pulmonary vascular reactivity in **transgenic mice**. Isolated perfused mouse lungs were used to evaluate the effect of selective loss of pulmonary nNOS, **iNOS**, and eNOS with respect to hypoxic pulmonary vasoconstriction (HPV) and endothelium-dependent and -independent vasodilation. eNOS null mice had augmented HPV (225 +/- 65% control, P < 0.02, mean +/- SE) and absent endothelium-dependent vasodilation, whereas endothelium-independent vasodilation was preserved. HPV was minimally elevated in **iNOS** null mice and normal in nNOS null mice. Both nNOS and **iNOS** null mice had normal endothelium-dependent vasodilation. In wild-type lungs, nonselective NOS inhibition doubled HPV, whereas selective **iNOS** inhibition had no detectable effect. In intact, lightly sedated mice, right ventricular systolic pressure was elevated in eNOS-deficient (42.3 +/- 1.2 mmHg, P < 0.001) and, to a lesser extent, in **iNOS**-deficient (37.2 +/- 0.8 mmHg, P < 0.001) mice, whereas it was normal in nNOS-deficient mice (30.9 +/- 0.7 mmHg, P = not significant) compared with wild-type controls (31.3 +/- 0.7 mmHg). We conclude that in the normal murine pulmonary circulation 1) nNOS does not modulate tone, 2) eNOS-derived nitric oxide is the principle mediator of endothelium-dependent vasodilation in the pulmonary circulation, and 3) both eNOS and **iNOS** play a role in modulating basal tone chronically.

L14 ANSWER 65 OF 86 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1999:695374 SCISEARCH
THE GENUINE ARTICLE: 233KB
TITLE: Relative contributions of endothelial, inducible, and neuronal NOS to tone in the murine pulmonary circulation
AUTHOR: Fagan K A (Reprint); Tyler R C; Sato K; Fouty B W; Morris K G; Huang P L; McMurtry F; Rodman D R
CORPORATE SOURCE: BOX C-272, 4200 E 9TH AVE, DENVER, CO 80262 (Reprint); UNIV COLORADO, HLTH SCI CTR, CARDIOVASC PULM RES LAB,

DENVER, CO 80262; UNIV COLORADO, HLTH SCI CTR, DEPT PHYSIOL, DENVER, CO 80262; HARVARD UNIV, SCH MED, BOSTON, MA 02114
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-LUNG CELLULAR AND MOLECULAR PHYSIOLOGY, (SEP 1999) Vol. 21, No. 3, pp. L472-L478. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 1040-0605.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 30

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Nitric oxide plays an important role in modulating pulmonary vascular tone. All three isoforms of nitric oxide synthase (NOS), neuronal (nNOS, NOS I), inducible (**iNOS**, NOS II), and endothelial (eNOS, NOS III), are expressed in the lung. Recent reports have suggested an important role for eNOS in the modulation of pulmonary vascular tone chronically; however, the relative contribution of the three isoforms to,acute modulation of pulmonary vascular tone is uncertain. We therefore tested the effect of targeted disruption of each isoform on pulmonary vascular reactivity in **transgenic mice**. Isolated perfused mouse lungs were used to evaluate the effect of selective loss of pulmonary nNOS, **iNOS**, and eNOS with respect to hypoxic pulmonary vasoconstriction (HPV) and endothelium-dependent and -independent vasodilation. eNOS null mice had augmented HPV (225 +/- 65% control, P < 0.02, mean +/- SE) and absent endothelium-dependent vasodilation, whereas endothelium-independent vasodilation was preserved. HPV was minimally elevated in **iNOS** null mice and normal in nNOS null mice. Both nNOS and **iNOS** null mice had normal endothelium-dependent vasodilation. In wild-type lungs, nonselective NOS inhibition doubled HPV, whereas selective **iNOS** inhibition had no detectable effect. In intact, lightly sedated mice, right ventricular systolic pressure was elevated in eNOS-deficient (42.3 +/- 1.2 mmHg, P < 0.001) and, to a lesser extent, in **iNOS**-deficient (37.2 +/- 0.8 mmHg, P < 0.001) mice, whereas it was normal in nNOS-deficient mice (30.9 +/- 0.7 mmHg, P = not significant) compared with wild-type controls (31.3 +/- 0.7 mmHg). We conclude that in the normal murine pulmonary circulation 1) nNOS does not modulate tone, 2) eNOS-derived nitric oxide is the principle mediator of endothelium-dependent vasodilation in the pulmonary circulation, and 3) both eNOS and **iNOS** play a role in modulating basal tone chronically.

L14 ANSWER 66 OF 86 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 39
ACCESSION NUMBER: 2000:54997 CAPLUS
DOCUMENT NUMBER: 132:346435
TITLE: Involvement of CD14 in LPS-induced liver injury in Propionibacterium acnes-primed mice
AUTHOR(S): Matsuura, Keiko; Kataoka, Masashi; Higuchi, Yasunori; Tamura, Yoichi; Akizuki, Shin'ichiro; Yamamoto, Shunsuke
CORPORATE SOURCE: Department of Pathology, Oita Medical University, Oita, 879-5503, Japan
SOURCE: Journal of Endotoxin Research (1999), 5(4), 227-230 CODEN: JENREB; ISSN: 0968-0519
PUBLISHER: Maney Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The size of granulomas induced by an i.p. administration of Propionibacterium acnes in M14M mice 7 days after priming was smaller than that in non-transgenic mice. The no. of CD14-pos. cells in granulomas was fewer in M14M mice than in non-transgenic mice. An LPS challenge induced apoptotic and necrotic changes in hepatocytes in non-transgenic mice but not in M14M mice. TNF.alpha. expression was found in monocytic cells in

granulomas and Kupffer cells in non-transgenic mice 7 days after priming and was significantly upregulated after LPS injection, whereas the expression was very low in these cells in M14M mice. The expression of IFN-.gamma., IL-12 and **iNOS** mRNAs produced by LPS challenge in M14M mice were low compared with those in non-**transgenic mice**. IL-18 mRNA expression was upregulated in P. acnes-primed nontransgenic mice but not in M14M mice. The prodn. of sCD14 was increased by both P. acnes priming and LPS challenge. The high sCD14 concn. may account for lethality without liver damage in M14M mice. The levels of ELAM-1 mRNA expression in several organs in M14M mice 1-3 h after LPS challenge were, however, lower than those in non-transgenic mice.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 67 OF 86 MEDLINE DUPLICATE 40
ACCESSION NUMBER: 1999110808 MEDLINE
DOCUMENT NUMBER: 99110808 PubMed ID: 9892605
TITLE: Interleukin 12 protects from a T helper type 1-mediated autoimmune disease, experimental autoimmune uveitis, through a mechanism involving interferon gamma, nitric oxide, and apoptosis.
AUTHOR: Tarrant T K; Silver P B; Wahlsten J L; Rizzo L V; Chan C C; Wiggert B; Caspi R R
CORPORATE SOURCE: Laboratory of Immunology, National Institutes of Health, Bethesda, Maryland 20892, USA.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1999 Jan 18) 189 (2) 219-30.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311
Entered Medline: 19990223

AB Pathogenic effector T cells in experimental autoimmune uveitis (EAU) are T helper type 1-like, and interleukin (IL)-12 is required for their generation and function. Therefore, we expected that IL-12 administration would have disease-enhancing effects. Mice were immunized with a uveitogenic regimen of the retinal antigen interphotoreceptor retinoid-binding protein, treated with IL-12 (100 ng/d for 5 d), and EAU was assessed by histopathology. Unexpectedly, IL-12 treatment failed to enhance EAU in resistant strains and downregulated disease in susceptible strains. Only treatment during the first, but not during the second, week after immunization was consistently protective. High levels of interferon gamma (IFN-gamma) were present in the serum during IL-12 treatment, but subsequent antigen-specific IFN-gamma production in protected mice was diminished, as were IL-5 production, lymph node cell proliferation, and serum antibody levels. Treated mice had fewer cells and evidence of enhanced apoptosis in the draining lymph nodes. Unlike wild-type mice, IFN-gamma-deficient, **inducible nitric oxide synthase** (**iNOS**)-deficient, and Bcl-2(lck) **transgenic mice** were poorly protected by IL-12, whereas IL-10-deficient mice were protected. We conclude that administration of IL-12 aborts disease by curtailing development of uveitogenic effector T cells. The data are compatible with the interpretation that IL-12 induces systemic hyperinduction of IFN-gamma, causing activation of **iNOS** and production of NO, which mediates protection at least in part by triggering Bcl-2 regulated apoptotic deletion of the antigen-specific T cells as they are being primed.

L14 ANSWER 68 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 41

ACCESSION NUMBER: 1999:282194 BIOSIS
DOCUMENT NUMBER: PREV199900282194
TITLE: Upregulation of **inducible nitric oxide synthase** in the spinal cord of a **transgenic mouse** model of familial ALS.
AUTHOR(S): Przedborski, Serge (1); Almer, Gabriele (1); Vukosavic, Slobodanka (1)
CORPORATE SOURCE: (1) New York, NY USA
SOURCE: Neurology, (April 12, 1999) Vol. 52, No. 6 SUPPL. 2, pp. A177.
Meeting Info.: 51st Annual Meeting of the American Academy of Neurology Toronto, Ontario, Canada April 17-24, 1999 American Academy of Neurology
. ISSN: 0028-3878.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 69 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:540801 BIOSIS
DOCUMENT NUMBER: PREV199900540801
TITLE: Heart failure induced by conditional overexpression of inducible NO-synthase (**iNOS**) targeted to the heart of **transgenic mice**.
AUTHOR(S): Mungrue, I. (1); Hussain, M. (1); Stewart, D. J. (1)
CORPORATE SOURCE: (1) The Terrence Donnelly Vascular Biology Laboratory, St. Michael's Hospital and The Toronto Hospital, University of Toronto, Toronto Canada
SOURCE: Acta Physiologica Scandinavica, (Sept., 1999) Vol. 167, No. SUPPL. 645, pp. 33.
Meeting Info.: Scientific Committees of the Sixth International Meeting on Biology of Nitric Oxide Stockholm, Sweden September 5-8, 1999 Scandinavian Physiological Society
. ISSN: 0001-6772.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 70 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:24370 BIOSIS
DOCUMENT NUMBER: PREV200000024370
TITLE: Myocardial overexpression of human **inducible nitric oxide synthase** (**iNOS**) in **transgenic mice** is cardiotoxic.
AUTHOR(S): Mungrue, Imran N. (1); Stewart, Duncan J.; You, Xiaomang; Azad, Azar; Husain, Mansoor
CORPORATE SOURCE: (1) Univ of Toronto, Toronto, ON Canada
SOURCE: Circulation, (Nov. 2, 1999) Vol. 110, No. 18 SUPPL., pp. I.112.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 71 OF 86 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 42
ACCESSION NUMBER: 1999:3332 CAPLUS
DOCUMENT NUMBER: 130:61994
TITLE: **Transgenic mouse** deficient in **inducible nitric oxide synthase** and methods of producing them
INVENTOR(S): MacMicking, John; Nathan, Carl; Mudgett, John S.
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA; Merck & Co Inc
SOURCE: U.S., 17 pp., Cont. of U.S. Ser. No. 284,898, abandoned.

CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5850004	A	19981215	US 1997-808191	19970228

PRIORITY APPLN. INFO.: US 1994-284898 19940802

AB The present invention provides an **inducible nitric oxide synthase** ("**iNOS**")-deficient **transgenic mouse**, novel replacement vectors designed for the disruption of the **iNOS** gene, embryonic stem (ES) cells which are singly allelic relative to the deficient **iNOS** locus, a host cell line or cell clone carrying a congenitally altered **iNOS** gene, and a method of producing such a **transgenic mouse** . The **iNOS**-deficient **transgenic mice** can be used to evaluate and/or test their susceptibility to infectious or tumorigenic challenge, autoimmunity, septic shock and inflammatory and allergic diseases.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 72 OF 86 MEDLINE DUPLICATE 43
ACCESSION NUMBER: 1999030655 MEDLINE
DOCUMENT NUMBER: 99030655 PubMed ID: 9811886
TITLE: Impaired liver regeneration in inducible nitric oxide synthasedeficient mice.
AUTHOR: Rai R M; Lee F Y; Rosen A; Yang S Q; Lin H Z; Koteish A; Liew F Y; Zaragoza C; Lowenstein C; Diehl A M
CORPORATE SOURCE: Department of Medicine, The Johns Hopkins University, Baltimore, MD 21205, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Nov 10) 95 (23) 13829-34. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981216

AB The mechanisms that permit adult tissues to regenerate when injured are not well understood. Initiation of liver regeneration requires the injury-related cytokines, tumor necrosis factor (TNF) alpha and interleukin (IL) 6, and involves the activation of cytokine-regulated transcription factors such as NF-kappabeta and STAT3. During regeneration, TNFalpha and IL-6 promote hepatocyte viability, as well as proliferation, because interventions that inhibit either cytokine not only block hepatocyte DNA synthesis, but also increase liver cell death. These observations suggest that the cytokines induce hepatoprotective factors in the regenerating liver. Given evidence that nitric oxide can prevent TNF-mediated activation of the pro-apoptotic protease caspase 3 and protect hepatocytes from cytokine-mediated death, cytokine-**inducible nitric oxide synthase** (**iNOS**) may be an important hepatoprotective factor in the regenerating liver. In support of this hypothesis we report that the hepatocyte proliferative response to partial liver resection is severely inhibited in **transgenic mice** with targeted disruption of the **iNOS** gene. Instead, partial hepatectomy is followed by increased caspase 3 activity, hepatocyte death, and liver failure, despite preserved induction of TNFalpha, IL-6, NF-kappabeta, and STAT3. These results suggest that during successful tissue regeneration, injury-related

cytokines induce factors, such as **iNOS** and its product, NO, that protect surviving cells from cytokine-mediated death.

L14 ANSWER 73 OF 86 MEDLINE DUPLICATE 44
ACCESSION NUMBER: 1998266170 MEDLINE
DOCUMENT NUMBER: 98266170 PubMed ID: 9605134
TITLE: Alternative metabolic states in murine macrophages reflected by the nitric oxide synthase/arginase balance: competitive regulation by CD4+ T cells correlates with Th1/Th2 phenotype.
AUTHOR: Munder M; Eichmann K; Modolell M
CORPORATE SOURCE: Max Planck Institut fur Immunobiologie, Freiburg, Germany.
SOURCE: JOURNAL OF IMMUNOLOGY, (1998 Jun 1) 160 (11) 5347-54. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980618
Last Updated on STN: 19980618
Entered Medline: 19980611

AB Activated murine macrophages metabolize L-arginine via two main pathways that are catalyzed by the inducible enzymes nitric oxide synthase (**iNOS**) and arginase. We have previously shown that CD4+ T cell-derived cytokines regulate a competitive balance in the expression of both enzymes in macrophages; Th1-type cytokines induce **iNOS** while they inhibit arginase, whereas the reverse is the case for Th2-type cytokines. Here we addressed the regulation of both metabolic pathways by CD4+ T cells directly. Macrophages were used as APCs for established Th1 and Th2 T cell clones as well as for in vitro polarized Th1 or Th2 T cells of **transgenic mice** bearing an MHC class II-restricted TCR. Both systems revealed a similar dichotomy in the macrophages; Th1 T cells led to an exclusive induction of **iNOS**, whereas Th2 T cells up-regulated arginase without inducing **iNOS**. Arginase levels induced by Th2 T cells far exceeded those inducible by individual Th2 cytokines. Similarly, high arginase levels could be induced by supernatants of Th2 cells stimulated in various ways. Ab blocking experiments revealed the critical importance of IL-4 and IL-10 for arginase up-regulation. Finally, strong synergistic effects between IL-4/IL-13 and IL-10 were observed, sufficient to account for the extraordinarily high arginase activity induced by Th2 cells. Our results suggest that the **iNOS**/arginase balance in macrophages is competitively regulated in the context of Th1- vs Th2-driven immune reactions, most likely by cytokines without the requirement for direct cell interaction.

L14 ANSWER 74 OF 86 MEDLINE DUPLICATE 45
ACCESSION NUMBER: 1999062257 MEDLINE
DOCUMENT NUMBER: 99062257 PubMed ID: 9844128
TITLE: Peroxynitrite formation and apoptosis in transgenic sickle cell mouse kidneys.
AUTHOR: Bank N; Kiroycheva M; Ahmed F; Anthony G M; Fabry M E; Nagel R L; Singhal P C
CORPORATE SOURCE: Renal and Hematology Divisions, Department of Medicine, Montefiore Medical Center, and the Albert Einstein College of Medicine and Long Island Jewish Medical Center, Bronx, New York, USA.
CONTRACT NUMBER: 2RO1 DA06753 (NIDA)
HL 38655 (NHLBI)
SOURCE: KIDNEY INTERNATIONAL, (1998 Nov) 54 (5) 1520-8. Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990211

AB BACKGROUND: In a previous study, nitric oxide synthases (NOS) were found to be strongly expressed in the tubular epithelium of kidneys of a **transgenic mouse** model of sickle cell disease (alphaHbetaS[betaMDD]). Because NOS activity is often associated with peroxynitrite formation when superoxide radical (.O-2) is present in abundance, we examined the kidneys of sickle cell mice for nitrotyrosine, considered to be a footprint of ONOO-. METHODS: Western blot and immunohistochemistry for nitrotyrosine was carried out. Since peroxynitrite and other reactive oxygen radicals are capable of causing apoptosis, we also performed agarose gel electrophoresis of kidney DNA and TUNEL staining of nuclei, indicators of apoptosis. RESULTS: Nitration of tyrosine residues of three proteins (kD 66, 57 and 22) was found on Western blot of kidney protein extracts of the sickle cell mice. The degree of tyrosine nitration of the 66 kD protein was not significantly different in the control versus **transgenic mice**, whereas tyrosine nitration of the 57 and 22 kD proteins was clearly increased in **transgenic mice**. Strong immunostaining for nitrotyrosine was seen in tubular epithelial cells of the sickle cell mice, in close proximity to positive immunostaining of **iNOS**. Neither **iNOS** nor nitrotyrosine was expressed in the control mice. DNA "laddering" was found localized to the same zones of the kidney as nitrotyrosine and **iNOS** immunostaining. TUNEL assay on mouse kidney tissue sections showed minimal tubular cell apoptosis in normal mouse with hypoxia, mild tubular cell apoptosis in sickle cell mouse in room air, and moderate tubular cell apoptosis in sickle cell mouse with hypoxia. CONCLUSIONS: The observations suggest that ONOO- and perhaps other reactive oxygen species are being produced in the sickle cell kidney. The mechanism may be ischemia/reperfusion due to intermittent vascular occlusion by sickle cells. The resulting hypoxia could result in **iNOS** activation, superoxide radical and peroxynitrite formation. Two consequences of these reactions appear to be nitration of tyrosine residues of some renal proteins and enhanced apoptosis.

L14 ANSWER 75 OF 86 MEDLINE DUPLICATE 46
ACCESSION NUMBER: 1998353543 MEDLINE
DOCUMENT NUMBER: 98353543 PubMed ID: 9687535
TITLE: Interleukin 12-mediated prevention of spontaneous mammary adenocarcinomas in two lines of Her-2/neu transgenic mice.
AUTHOR: Boggio K; Nicoletti G; Di Carlo E; Cavallo F; Landuzzi L; Melani C; Giovarelli M; Rossi I; Nanni P; De Giovanni C; Bouchard P; Wolf S; Modesti A; Musiani P; Lollini P L; Colombo M P; Forni G
CORPORATE SOURCE: Department of Clinical and Biological Sciences, University of Turin, 10043 Orbassano, Italy.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Aug 3) 188 (3) 589-96.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 20000303
Entered Medline: 19980908

AB The ability of interleukin (IL)-12 to prevent tumors when administered to individuals with a genetic risk of cancer was studied in two lines of **transgenic mice** expressing rat HER-2/neu oncogene in the mammary gland. Female BALB/c (H-2(d)) mice carrying the activated HER-2/neu oncogene show no morphological abnormalities of the mammary gland

until 3 wk of age. They then progress through atypical hyperplasia to in situ lobular carcinoma and at 33 wk of age all 10 mammary glands display invasive carcinomas. Adult FVB mice (H-2(q)) carrying the HER-2/neu protooncogene develop mammary carcinomas with a longer latency (38-49 wk) and a lower multiplicity (mean of 2.6 tumors/mice). Treatment with IL-12 (5 daily intraperitoneal injections, 1 wk on, 3 wk off; the first course with 50 ng IL-12/day, the second with 100 ng IL-12/day) begun at 2 wk of age in BALB/c mice and at 21 wk of age in FVB mice markedly delayed tumor onset and reduced tumor multiplicity. Analogous results were obtained in immunocompetent and permanently CD8(+) T lymphocyte-depleted mice. In both transgenic lines, tumor inhibition was associated with mammary infiltration of reactive cells, production of cytokines and **inducible nitric oxide synthase**, and reduction in microvessel number, in combination with a high degree of hemorrhagic necrosis.

L14 ANSWER 76 OF 86 MEDLINE DUPLICATE 47
ACCESSION NUMBER: 1999108167 MEDLINE
DOCUMENT NUMBER: 99108167 PubMed ID: 9888990
TITLE: Interferon-gamma in progression to chronic demyelination and neurological deficit following acute EAE.
AUTHOR: Renno T; Taupin V; Bourbonniere L; Verge G; Tran E; De Simone R; Krakowski M; Rodriguez M; Peterson A; Owens T
CORPORATE SOURCE: Neuroimmunology Unit, Montreal Neurological Institute, 3801 University, Montreal, Quebec, H3A 2B4, Canada.
SOURCE: MOLECULAR AND CELLULAR NEUROSCIENCES, (1998 Dec) 12 (6) 376-89.
Journal code: 9100095. ISSN: 1044-7431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 20000303
Entered Medline: 19990212

AB The cytokine interferon-gamma (IFNgamma) is implicated in the induction of acute CNS inflammation, but it is less clear what role if any IFNgamma plays in progression to chronic demyelination and neurological deficit. To address this issue, we have expressed IFNgamma in myelinating oligodendrocytes of **transgenic mice**. MHC I immunostaining and **iNOS** mRNA were upregulated in their CNS, but such **transgenic mice** showed no spontaneous CNS inflammation or demyelination, and the incidence, severity, and histopathology of experimental autoimmune encephalomyelitis (EAE) were similar to nontransgenic controls. In contrast to control mice, which remit from EAE with resolution of glial reactivity and leukocytic infiltration, transgenics showed chronic neurological deficits. While activated microglia/macrophages persisted in demyelinating lesions for over 100 days, CD4(+) T lymphocytes were no longer present in CNS. IFNgamma therefore may play a role in chronic demyelination and long-term disability following the induction of demyelinating disease. Because IFNgamma may have neural as well as immune-infiltrating origins, these findings generate a new perspective on its role in the CNS.

L14 ANSWER 77 OF 86 BIOSIS
ACCESSION NUMBER: 1999:9240 BIOSIS
DOCUMENT NUMBER: PREV199900009240
TITLE: Inducible no synthase (**iNOS**) contributes to blood pressure regulation in ET-1 **transgenic mice**.
AUTHOR(S): Hocher, B. (1); Schwarz, A.; Slowinski, T. (1); Thone-Reineke, C.; George, I.; Bauer, C.; Neumayer, H. H. (1); Theuring, F.

CORPORATE SOURCE: (1) Dep. Nephrol., Charite, HU Berlin, Berlin Germany
SOURCE: Journal of the American Society of Nephrology, (Sept., 1998) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 339A. Meeting Info.: 31st Annual Meeting of the American Society of Nephrology Philadelphia, Pennsylvania, USA October 25-28, 1998 American Society of Nephrology . ISSN: 1046-6673.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 78 OF 86 MEDLINE DUPLICATE 48
ACCESSION NUMBER: 1999008956 MEDLINE
DOCUMENT NUMBER: 99008956 PubMed ID: 9790729
TITLE: Sca1(+)/Mac1(+) nitric oxide-producing cells in the spleens of recipients early following bone marrow transplant suppress T cell responses in vitro.
AUTHOR: Johnson B D; Hanke C A; Becker E E; Truitt R L
CORPORATE SOURCE: Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, 53226, USA.
CONTRACT NUMBER: CA39854 (NCI)
SOURCE: CELLULAR IMMUNOLOGY, (1998 Nov 1) 189 (2) 149-59. Journal code: 1246405. ISSN: 0008-8749.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981124

AB Spleen cells collected from allogeneic chimeras early after bone marrow transplantation (BMT) consistently showed suppressed proliferative responses to interleukin-2 in vitro and failed to proliferate in mixed lymphocyte reaction (MLR) assays. However, isolation of Thy 1.2(+) T cells from the heterogeneous spleen cell suspension prior to culture resulted in heightened proliferation, suggesting the presence of cells capable of suppressing T cell responses in vitro. When separated into subpopulations by negative and positive selection with specific monoclonal antibodies, a non-T, non-B population with immunosuppressive properties was identified. The suppressive cells were found in the spleens of both allogeneic and syngeneic chimeras, but not normal donor mice. Suppressor activity was transient and typically declined by 3 weeks post-BMT. The cells suppressed the response of alloactivated T cells isolated from BMT chimeras as well as naive donor T cells in MLR assays in a dose-dependent manner. To explore the mechanism(s) involved in the suppression, the effects of interferon-gamma (IFN-gamma)-specific mAb and the nitric oxide (NO) synthase inhibitor NG-methyl-l-arginine were examined. The results support a role for both IFN-gamma and NO in the suppressive activity. Separation of cells based on Mac-1 expression indicated that there were both Mac-1-enriched and Mac-1-depleted cells capable of producing NO, but that the Mac-1-depleted cells were the most potent suppressors in MLR assays. The Mac-1-depleted cells still contained a residual population of Mac-1(dim) cells which showed increased levels of Mac-1 expression after overnight culture. Intracellular staining with an **inducible nitric oxide synthase** (**iNOS**)-specific mAb indicated that the NO-producing cells expressed the cell surface markers Mac-1 and Sca-1. When **iNOS** knockout **transgenic mice** were used as transplant donors, in vitro suppression of T cell responses was reduced but not eliminated, suggesting that other mechanism(s) could contribute to the suppression. Collectively, these results demonstrate that Sca-1(+)/Mac-1(+) cells capable of producing NO are present in the spleens of recipients early after BMT and suggest that these cells may have immunoregulatory roles in vivo.

L14 ANSWER 79 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:111210 BIOSIS
DOCUMENT NUMBER: PREV199900111210
TITLE: Inducible NO synthase (**iNOS**) contributes to blood pressure regulation in ET-1 **transgenic mice**.
AUTHOR(S): Hocher, B. (1); Schwarz, A. (1); Slowinski, T. (1); Neumayer, H. H. (1); Bauer, C.; Bachmann, S.; Pfeilschifter, J.; Theuring, F.
CORPORATE SOURCE: (1) Dep. Nephrology, Charite, HU, Berlin Germany
SOURCE: Kidney & Blood Pressure Research, (1998) Vol. 21, No. 2-4, pp. 110.
Meeting Info.: Congress of Nephrology 1998 Joint Scientific Meeting of the Society Nephrology Erlangen, Germany September 19-22, 1998 The Society for Nephrology
. ISSN: 1420-4096.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 80 OF 86 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 1997038683 PCTFULL ED 20020514
TITLE (ENGLISH): NITRONE FREE RADICAL TRAP TREATMENT OF DEMENTIA ASSOCIATED WITH AIDS VIRUS (HIV-1) INFECTION
TITLE (FRENCH): TRAITEMENT DE LA DEMENCE ASSOCIEE A L'INFECTION PAR LE VIRUS DU SIDA (VIH-1) AU MOYEN DE PIEGES A RADICAUX LIBRES A BASE DE NITRONE
INVENTOR(S): FLOYD, Robert; GARLAND, William
PATENT ASSIGNEE(S): OKLAHOMA MEDICAL RESEARCH FOUNDATION; CENTAUR PHARMACEUTICALS, INC.; FLOYD, Robert; GARLAND, William
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9738683	A1	19971023
DESIGNATED STATES	AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1997-US6253	A	19970417
PRIORITY INFO.:	US 1996-60/015,709		19960417

ABEN Nitrone-based free radical traps are disclosed to have activity as therapeutic and prophylactic agents in the treatment of neuronal damage associated with HIV-1 virus infection, referred to in advanced stages as dementia associated with AIDS infection or AIDS Dementia Complex (ADC).

ABFR L'invention concerne des pieges a radicaux libres a base de nitrone, qui sont utiles en tant qu'agents therapeutiques et prophylactiques dans le traitement de lesions des cellules nerveuses associees a l'infection par le virus HIV-1, connues a des stades plus avances sous le nom de demence associee a l'infection par le virus du sida, ou complexe de demence liee au sida.

L14 ANSWER 81 OF 86 MEDLINE DUPLICATE 49
ACCESSION NUMBER: 97326542 MEDLINE
DOCUMENT NUMBER: 97326542 PubMed ID: 9183363
TITLE: Nitric oxide synthase in models of focal ischemia.
AUTHOR: Samdani A F; Dawson T M; Dawson V L
CORPORATE SOURCE: Department of Neurology, Johns Hopkins University School of

Medicine, Baltimore, MD 21287, USA.
CONTRACT NUMBER: NS 01578 (NINDS)
NS 33142 (NINDS)
NS 33277 (NINDS)
SOURCE: STROKE, (1997 Jun) 28 (6) 1283-8. Ref: 58
Journal code: 0235266. ISSN: 0039-2499.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970716
Last Updated on STN: 20000303
Entered Medline: 19970701

AB BACKGROUND AND PURPOSE: Cessation of blood flow to the brain, for even a few minutes, sets in motion a potential reversible cascade of events resulting in neuronal cell death. Oxygen free radicals and oxidants appear to play an important role in central nervous system injury after cerebral ischemia and reperfusion. Recently, divergent roles for the newly identified neuronal messenger molecule and oxygen radical, nitric oxide (NO), have been identified in various models of cerebral ischemia. Because of the chemical and physical properties of NO, the numerous physiological activities it mediates, and the lack of specific agents to modulate the activity of the different isoforms of NO synthase (NOS), reports regarding the role of NO in focal cerebral ischemia have been confounding and often conflicting. Recent advances in pharmacology and the development of transgenic knockout mice specific for the different isoforms of NOS have advanced our knowledge and clarified the role of NO in cerebral ischemia. METHODS: Animal models of focal ischemia employ occlusion of nutrient cerebral vessels, most commonly the middle cerebral artery. Primary cortical cultures are exposed to excitotoxic or ischemic conditions, and the activities of NOS isoforms or NO production are evaluated. **Transgenic mice** lacking expression of either the neuronal isoform of NOS (nNOS), the endothelial isoform of NOS (eNOS), or the immunologic isoform of NOS (**iNOS**) have been examined in models of excitotoxic injury and ischemia. RESULTS: Excitotoxic or ischemic conditions excessively activate nNOS, resulting in concentrations of NO that are toxic to surrounding neurons. Conversely, NO generated from eNOS is critical in maintaining cerebral blood flow and reducing infarct volume. **iNOS**, which is not normally present in healthy tissue, is induced shortly after ischemia and contributes to secondary late-phase damage. CONCLUSIONS: Pharmacological and genetic approaches have significantly advanced our knowledge regarding the role of NO and the different NOS isoforms in focal cerebral ischemia. nNOS and **iNOS** play key roles in neurodegeneration, while eNOS plays a prominent role in maintaining cerebral blood flow and preventing neuronal injury.

L14 ANSWER 82 OF 86 MEDLINE DUPLICATE 50
ACCESSION NUMBER: 97460162 MEDLINE
DOCUMENT NUMBER: 97460162 PubMed ID: 9314587
TITLE: Expression of the inducible nitric oxide synthase gene in mouse uterine leukocytes and potential relationships with uterine function during pregnancy.
AUTHOR: Hunt J S; Miller L; Vassmer D; Croy B A
CORPORATE SOURCE: Department of Anatomy, University of Kansas Medical Center, Kansas City 66160-7400, USA.. jhunt@kumc.edu
CONTRACT NUMBER: HD02528 (NICHD)
HD24212 (NICHD)
SOURCE: BIOLOGY OF REPRODUCTION, (1997 Oct) 57 (4) 827-36.
Journal code: 0207224. ISSN: 0006-3363.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M84373
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19990129
Entered Medline: 19971121

AB Nitric oxide (NO), a potent and versatile free radical, is synthesized in leukocytes by the inducible form of NO synthase (**iNOS**). In this study, leukocytes in pregnant mouse uterus were investigated for expression of the **iNOS** gene. Inducible NOS mRNA, which was identified by reverse transcriptase polymerase chain reaction, was high relative to an invariant mRNA, glyceraldehyde-3-phosphate dehydrogenase, in midgestation uteri (gestation days [g.d.] 10, 12, and 14) but was low in late-gestation uteri (g.d. 16 and 18). Inducible NOS protein, identified immunohistochemically in paraformaldehyde-fixed uteri taken from g.d. 6 through 18 using rabbit antibodies generated to mouse carboxyl terminus **iNOS** peptides, was prominent in a few myometrial mast cells at early stages and was strongly expressed from g.d. 6 through g.d. 14 in myometrial macrophage-like cells. Inducible NOS protein was first detected in uterine (u) natural killer (NK) cells at g.d. 8. Signals peaked in this lineage at g.d. 10 and declined thereafter. Uterine leukocytes cultured in vitro expressed the **iNOS** gene; a hybridoma cell line derived from mouse uNK cells (GWM1-2) contained **iNOS** mRNA, and cells migrating from mouse metrial gland explants included **iNOS**/ leukocytes. Large, granular **iNOS** + uNK cells were absent from the uteri of homologously mated pregnant TgE26 mice, an NK cell-deficient **transgenic mouse** strain, but immunoreactive **iNOS** was detectable in trophoblast, a cell lineage that did not contain immunoreactive **iNOS** in NK cell-competent Swiss-Webster mice. In TgE26 mothers gestating normal embryos, the same pattern was observed. Collectively, the results of this study demonstrate that **iNOS** is present in mouse uterine leukocytes including mast cells, macrophage-like cells, and uNK cells, and suggest that in the absence of uNK cells, the placenta synthesizes **iNOS**. These findings are consistent with the postulate that leukocyte NO contributes importantly to events associated with successful pregnancy that are likely to include relaxation of vascular smooth muscle.

L14 ANSWER 83 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 51
ACCESSION NUMBER: 1997:183441 BIOSIS
DOCUMENT NUMBER: PREV199799482644
TITLE: **Inducible nitric oxide synthase** and cyclooxygenase are expressed in human-TNF-alpha **transgenic mice** which develop arthritis spontaneously.
AUTHOR(S): Platts, L. A. M. (1); Haralambous, S.; Hukkanen, M. V. J. (1); Gross, S. S.; Maclouf, J.; Kollias, G.; Polak, J. M. (1)
CORPORATE SOURCE: (1) Dep. Histochem., Royal Postgrad. Med. Sch., London W12 ONN UK
SOURCE: Journal of Pathology, (1997) Vol. 181, No. SUPPL., pp. 42A. Meeting Info.: 174th Meeting of the Pathological Society of Great Britain and Ireland London, England, UK January 8-10, 1997
ISSN: 0022-3417.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L14 ANSWER 84 OF 86 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 1996014748 PCTFULL ED 20020514
TITLE (ENGLISH): AMELIORATION OF HUMAN ERECTILE DYSFUNCTION BY TREATMENT WITH iNOS, AND RELATED NOS AGENTS
TITLE (FRENCH): AMELIORATION DES DYSFONCTIONNEMENTS ERECTILES CHEZ L'HOMME, PAR TRAITEMENT PAR MONOXYDE D'AZOTE SYNTHETASE

INDUCTIBLE (INOS) ET AGENTS NOS APPARENTES

INVENTOR(S): GONZALEZ-CADAVID, Nestor, F.; RAJFER, Jacob

PATENT ASSIGNEE(S): NIREC, INC.; GONZALEZ-CADAVID, Nestor, F.; RAJFER, Jacob

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9614748	A1	19960523
DESIGNATED STATES	AL AM AU BB BG BR BY CA CN CZ EE FI GE HU JP KP KR LK LR LT LV MD MK MX NO NZ PL RO RU SI SK TT UA US VN AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1995-US14588	A	19951109
PRIORITY INFO.:	US 1994-8/337,357		19941110

ABEN Treatment of erectile dysfunction comprising administering to a patient, inducible Nitric Oxide Synthase (iNOS) agents, including penile iNOS, inducers of penile iNOS, iNOS cDNA, or penile smooth muscle cells or corpora cavernosa with iNOS cDNA. Typical in vivo treatment involves delivery of these agents to the penile tissue of a patient by constant or intermittent implanted or external infusion pump, pellets, intrauretheral administration, injection or other related procedures. The genetically engineered cells or penile tissue from the patient hyperexpressing iNOS is implanted in microcapsules, pellets, or other methods, or directly by surgical inoculation into the corpora cavernosa. In certain cases, an oral or injectable systemic route of administration is applicable.

Also disclosed are methods of treatment involving in vitro induction of iNOS in cultured smooth muscle cells and thereofter delivery of purified or recombinant iNOS enzyme, production of iNOS cDNA and genetic transformation with iNOS cDNA, followed by delivery thereof to the penis of a patient.

The methods of this invention include hyperexpression and/or biological modulation of other endogenous and exogenous NOS isoforms in the penis, for the treatment of erectile dysfunction.

ABFR L'invention concerne le traitement des dysfonctionnements erectiles par administration au patient d'agents monoxyde d'azote synthetase inductible (iNOS), dont l'iNOS penienne, les inducteurs d'iNOS penienne, l'ADNc iNOS, ou par administration de cellules de muscles lisses peniens ou de corps caverneux avec de l'ADNc iNOS. Un traitement in vivo type consiste a administrer ces agents aux tissus peniens du patient a l'aide d'une pompe a perfusion constante ou intermittente implantee ou externe, par pellets par administration intra-uretrale, par injection ou par d'autres procedes apparentes. Les cellules ou les tissus peniens provenant du patient et transformes par genie genetique de maniere a hyper-exprimer l'iNOS sont implantes sous forme de microcapsules, de pellets ou par d'autres procedes, ou bien directement par inoculation chirurgicale dans les corps caverneux.

Dans certains cas, un mode systemique d'administration par voie orale ou par injection est possible.

L'invention concerne en outre des procedes de traitement impliquant l'induction in vivo d'iNOS dans des cellules de muscles lisses peniens, mises en culture, puis l'administration de l'enzyme d'iNOS

purifiee ou recombinee, la production d'ADNc iNOS et la transformation par ADNc iNOS, suivie de son
administration au patient. Les procedes de cette invention comprennent l'hyperexpression et/ou la
modulation biologique d'autres isoformes endogenes et exogenes de NOS, dans le penis, pour traiter
les dysfonctionnements erectiles.

L14 ANSWER 85 OF 86 MEDLINE DUPLICATE 52
ACCESSION NUMBER: 96401211 MEDLINE
DOCUMENT NUMBER: 96401211 PubMed ID: 8807587
TITLE: Renal nitric oxide synthases in transgenic sickle cell mice.
AUTHOR: Bank N; Aynedjian H S; Qiu J H; Osei S Y; Ahima R S; Fabry M E; Nagel R L
CORPORATE SOURCE: Department of Medicine, Montefiore Medical Center, Bronx, New York, USA.
CONTRACT NUMBER: HL 38655 (NHLBI)
SOURCE: KIDNEY INTERNATIONAL, (1996 Jul) 50 (1) 184-9.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961122

AB The alpha H beta S [beta MDD] mouse is a useful model for studying renal functional abnormalities in sickle cell disease. We previously reported that these mice develop a urine concentrating defect when chronically exposed to a low oxygen environment. In the present study, we measured glomerular filtration rate (GFR), urinary excretion of NO2 s+ NO3, the stable products of nitric oxide (NO), and the abundance of endothelial constitutive nitric oxide synthase (NOS III) and **inducible nitric oxide synthase** (NOS II) in the kidneys by Western blot. Immunohistochemistry was also carried out. We found that GFR is significantly higher in the **transgenic mice** than in controls. The urinary NO2 + NO3/creatinine ratio was also higher. The Western blots revealed that both NOS III and NOS II are markedly increased in the kidneys of **transgenic mice** as compared to normal control mice. Immunohistochemistry localized NOS III reactivity in proximal convoluted cells in the cortex of control and alpha H beta S [beta MDD] mice. NOS II immunostaining was not seen in control mice but was clearly evident in glomeruli and distal nephron segments of the alpha H beta S [beta MDD] mice. These observations suggest that NOS II is induced in glomeruli and distal nephrons of the alpha H beta S [beta MDD] mice. An increase in synthesis of NO may occur in the glomeruli as a result of NOS II induction, and this may contribute to the hyperfiltration in these mice.

L14 ANSWER 86 OF 86 MEDLINE DUPLICATE 53
ACCESSION NUMBER: 95220183 MEDLINE
DOCUMENT NUMBER: 95220183 PubMed ID: 7535683
TITLE: Reactive gliosis as a consequence of interleukin-6 expression in the brain: studies in transgenic mice.
AUTHOR: Chiang C S; Stalder A; Samimi A; Campbell I L
CORPORATE SOURCE: Department of Neuropharmacology, Scripps Research Institute, La Jolla, Calif. 92037.
CONTRACT NUMBER: MH 47680 (NIMH)
MH 50426 (NIMH)
SOURCE: DEVELOPMENTAL NEUROSCIENCE, (1994) 16 (3-4) 212-21.
Journal code: 7809375. ISSN: 0378-5866.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19960129
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AB Gliosis is a characteristic pathologic state in many CNS disorders. Cytokines are considered to be effectors of gliosis. In order to explore the role of IL-6 in gliosis, the temporal and spatial expression of the IL-6 gene and its consequent effects on the brain were studied in a GFAP-IL6 **transgenic mouse** model. In GFAP-IL6 mice, IL-6 transgene expression was detectable in the brain at 1 week postnatally and increased to maximal levels by 3 months of age before declining at 8 and 12 months. Enhanced glial fibrillary acidic protein (GFAP) (marker for astrocytes) and Mac-I (marker for microglia) mRNA expression were first prominent at 1 month, increased to maximum levels by 3 months and remained significantly elevated through 12 months of age. Western blot analysis revealed that the enhanced GFAP mRNA expression in these **transgenic mice** was accompanied by increased GFAP protein levels. Immunostaining for Mac-I demonstrated that in addition to an increased staining intensity, the number of cells expressing the microglial/macrophage marker was also apparently increased, particularly in the cerebellum and brain stem. Concurrent with IL-6 transgene mRNA expression and reactive gliosis, upregulation of IL-1 alpha/beta, TNF alpha, ICAM-1 and EB22/5.3 (acute-phase reactant) but not **inducible nitric oxide synthase** gene expression was also observed. EB22/5.3 mRNA expression was most prominent and increased progressively with age. Expression of the IL-6, GFAP and EB22/5.3 RNAs was found to have similar distribution in the brain being found predominantly in the cerebellum, brain stem and sub-cortical regions. In conclusion, the constitutive expression of IL-6 in the brain induced the development of a pronounced and lifelong reactive gliosis affecting both astrocytes and microglia. The altered state of these cells may contribute to the functional and structural CNS impairment exhibited by the GFAP-IL6 mice. Finally, in these mice, expression of the EB22/5.3 gene correlated closely with the progression of neuropathy indicating that this acute-phase response gene was a good marker for and may be involved in the pathogenesis of CNS injury mediated by the expression of IL-6.

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(FILE 'HOME' ENTERED AT 11:46:40 ON 03 FEB 2003)

FILE 'MEDLINE, PCTFULL, USPATFULL' ENTERED AT 11:46:56 ON 03 FEB 2003
L1 29514 S TRANSGENIC MOUSE
L2 9003 S INOS OR INDUCIBLE NITRIC OXIDE SYNTHASE OR INDUCIBLE NITRIC O
L3 59 S L1 (S) L2
L4 1638 S (KNOCKOUT OR DEFICINET) (S) L1
L5 1610 S HUMAN (S) L2
L6 2 S L4 (S) L5
L7 9 S L4 (L) L5
L8 59 DUP REM L3 (0 DUPLICATES REMOVED)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, PCTFULL, USPATFULL, CONFSCI, SCISEARCH' ENTERED AT 11:54:36 ON 03 FEB 2003
L9 244 S L3
L10 9 S L6
L11 244 S L9
L12 16 S L7
L13 10 DUP REM L10 L12 (15 DUPLICATES REMOVED)
L14 86 DUP REM L11 (158 DUPLICATES REMOVED)

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